Clinical Study Protocol

INCB 18424-326

Topical **Ru**xolitinib **E**valuation in **A**topic **D**ermatitis Study (TRuE-AD4)

A Phase 3b, Double-Blind, Multicenter, Randomized, Vehicle-Controlled, Efficacy, and Safety Study of Ruxolitinib Cream in Adults With Moderate Atopic Dermatitis

Product:	**Ruxolitinib Cream**
IND Number:	[redacted]
EU CT Number:	**2023-505433-27-00**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**05 OCT 2023**
Amendment 1:	**30 NOV 2023**
Amendment 2:	**08 AUG 2024**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-326 Protocol Amendment 2 (dated 08 AUG 2024) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50/75/90	≥ 50%, ≥ 75%, or ≥ 90% improvement in Eczema Area and Severity Index score
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EEA	European Economic Area
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure

Abbreviations and Special Terms	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment Treatment Success (IGA score of 0 or 1 with ≥ 2-grade improvement from baseline)
IRB	institutional review board
IRT	interactive response technology
Itch NRS	Itch Numeric Rating Scale
ITCH2	≥ 2-point improvement in Itch Numeric Rating Scale score
ITCH4	≥ 4-point improvement in Itch Numeric Rating Scale score
ITT	intent-to-treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
PDE4	phosphodiesterase-4
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PP	per Protocol
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
ROW	rest of world
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORAD	SCORing Atopic Dermatitis
Skin Pain NRS	Skin Pain Numeric Rating Scale
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
SRM	Study Reference Manual
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid

Abbreviations and Special Terms	Definition
TEAE	treatment-emergent adverse event
Th	T-helper
TSQM-9	9-Item Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
US	United States
UV	ultraviolet
VC	vehicle-controlled
VCE	vehicle-controlled extension
WOCBP	women of childbearing potential
WPAI-AD	Work Productivity and Activity Impairment – Atopic Dermatitis

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 3b, Double-Blind, Multicenter, Randomized, Vehicle-Controlled, Efficacy, and Safety Study of Ruxolitinib Cream in Adults With Moderate Atopic Dermatitis

Protocol Number: INCB 18424-326

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Coprimary	
To establish the efficacy of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• Proportion of participants with EASI75 from baseline at Week 8. (EASI75 is defined as achieving ≥ 75% improvement in EASI score.) • Proportion of participants with IGA-TS at Week 8. (IGA-TS is defined as achieving an IGA score of 0 or 1 with ≥ 2 grade improvement from baseline.)
Key Secondary	
To further assess the treatment effects of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• Proportion of participants with ITCH4 from baseline to Week 8. (ITCH4 is defined as achieving ≥ 4-point improvement in Itch NRS score.) • Proportion of participants with ITCH4 from baseline to Day 7. • Proportion of participants with ITCH4 from baseline to Day 3. • Proportion of participants with ITCH4 from baseline to Day 2.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 3b
Clinical Indication	Treatment of adults with moderate AD
Population	Participants at least 18 years of age who have been diagnosed with moderate AD with a documented inadequate response, intolerance, or contraindication to TCSs and TCIs
Number of Participants	Approximately 225 participants will be randomized 2:1 to blinded treatment with ruxolitinib 1.5% cream BID or vehicle cream BID, with stratification by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW or Europe)
Study Design	Double-blind, multicenter, randomized, VC, efficacy, and safety study of ruxolitinib cream
Estimated Duration of Study Participation	Approximately 34 weeks: 28 (+ 7) days in the screening period, 8 weeks in the VC period, 16 weeks in the VCE period, and 30 (+ 7) days in the safety follow-up period
Data Safety Monitoring Board/Data Monitoring Committee	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

This is a Phase 3b, multicenter, randomized, double-blind, VC study, with the option of an escape arm for inadequate responders (< EASI50 at and after Week 8), in adult participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.

Participants will be randomized 2:1 to blinded treatment with ruxolitinib cream 1.5% BID or vehicle cream BID for an 8-week VC period. After completing 8 weeks of continuous treatment, all eligible participants with an adequate response, defined as achieving at least EASI50 from baseline, will continue blinded as needed treatment allocation and will be evaluated during an additional 16-week VCE period for durability of response. Participants will be eligible to enter the ruxolitinib 1.5% cream open-label escape arm if EASI50 is not achieved at Week 8 or if an EASI50 response from baseline is lost during the VCE period.

Following the EOT (Week 24 or ET), all participants will have a safety follow-up visit 30 days later (or 30 days after the last application of study treatment if the Week 24 or ET visit was not performed).

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

Figure 1: Study Design Schema

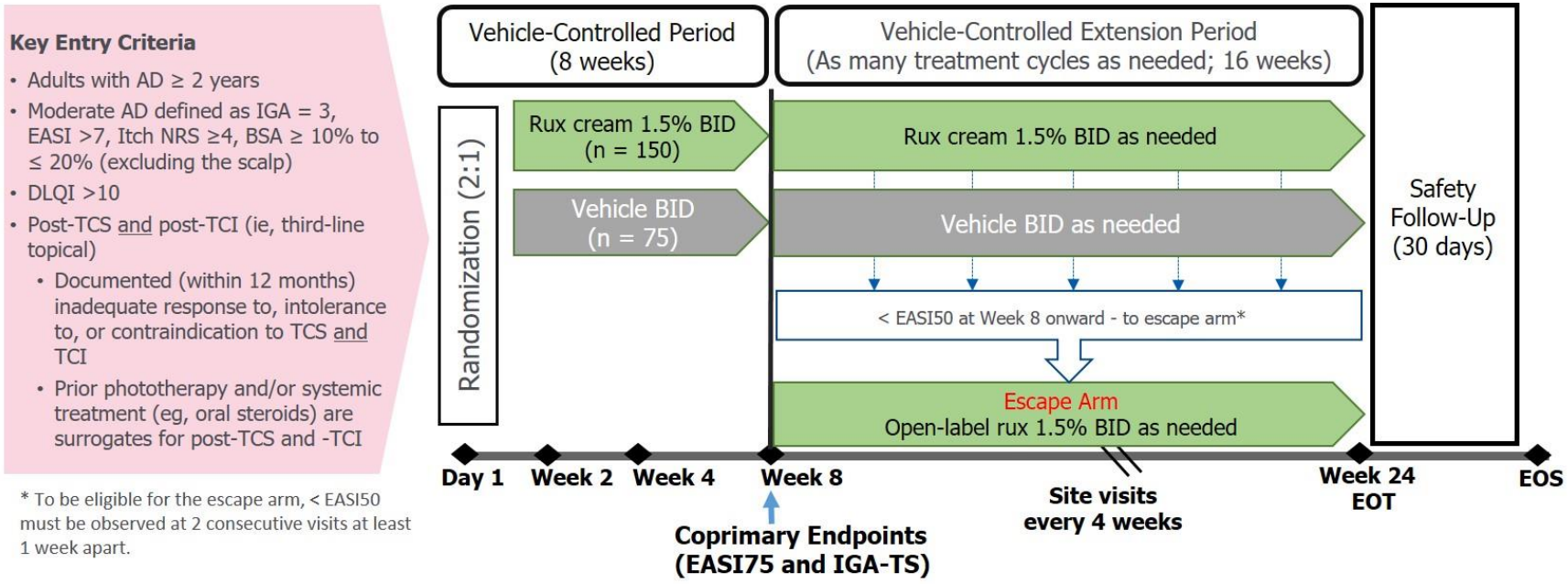


Table 3: Schedule of Activities: Vehicle-Controlled Period

Visit (Range)	Screening	VC Period[a]				Notes
	Days −28 to −1 (+ 7 d)[b]	Day 1[c] (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8[d] or ET1 (± 3 d)	
Administrative procedures						
Informed consent	X					Section 8.1.1.
Contact IRT	X	X	X	X	X	Section 8.1.3.
Inclusion/exclusion criteria	X	X				Section 5.
Demography and general medical history	X					Section 8.1.5.1.
Relevant AD medical history	X					Section 8.1.5.2.
Prior/concomitant medications and procedures	X	X	X	X	X	Section 6.6.
Apply study cream at site under direct site staff supervision		X	X	X	X*	Section 6.1.1. At the Day 1 visit, the participant should apply the first (morning) dose of study cream at the site. For all other visits, the participant should apply either of the 2 daily doses at the site, under site staff supervision, as long as the previous dose was applied at least 4 hours prior. *Not required if IGA score is 0 or at the ET1 visit.
Weigh/dispense study cream		X	X	X	X*	Section 6.4. New tubes of study cream will be provided at each visit. *Dispensing does not apply at an ET visit.
Collect/weigh returned study cream			X	X	X	Section 6.4.
Assess eDiary compliance	X	X	X	X	X	Section 6.4 and Section 8.1.4.
Assess study cream compliance			X	X	X	Section 6.4.
Contact participant at minimum 1 week prior to each study visit to confirm compliance with eDiary		X	X	X	X	Section 6.4 and Section 8.1.4. Note: AEs and concomitant medications can be recorded as well.

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

Visit (Range)	Screening	VC Period[a]				Notes
	Days −28 to −1 (+ 7 d)[b]	Day 1[c] (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8[d] or ET1 (± 3 d)	
Safety assessments						
AE assessments	X	X	X	X	X	Section 8.3.1 and Section 9.
Targeted physical examination		X	X	X	X	Section 8.3.2.2. Conducted only when indicated by symptoms reported by the participant, AEs, or other findings; clinically significant abnormalities (in the investigator's judgment) are to be reported as AEs.
Comprehensive physical examination	X				X*	Section 8.3.2.1. *ET1 visit only.
Body weight and height	X*	X	X	X	X	Section 8.3.3. *Height at screening only.
Vital signs	X	X	X	X	X	Section 8.3.3. To be taken before blood sampling and other procedures (not including all PROs).
PRO assessments						
Provide eDiary/PRO device and instructions	X					Section 8.1.4.
DLQI	X	X	X	X	X	Section 8.2.6. All PROs must be completed before any other evaluations (except those necessary prior to registration of visits in the IRT) or study procedures on the day of the study visit and prior to discussions with the investigator or study site staff.
POEM		X	X	X	X	
EQ-5D-5L		X	X	X	X	
HADS		X	X	X	X	
WPAI-AD		X			X	
PROMIS Short Form - Sleep-Related Impairment (8a) (7-day recall)		X	X	X	X	
PROMIS Short Form - Sleep Disturbance (8b) (7-day recall)		X	X	X	X	
TSQM-9			X		X	

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

Visit (Range)	Screening	VC Period[a]				Notes
	Days −28 to −1 (+ 7 d)[b]	Day 1[c] (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8[d] or ET1 (± 3 d)	
Efficacy assessments						
Evaluate %BSA affected by active AD	X	X	X	X	X	Section 8.2.2. Section 8.2.2.1. The presence of AD lesions in intertriginous regions should also be determined
IGA	X	X	X	X	X	Section 8.2.3.
EASI	X	X	X	X	X	Section 8.2.4.
SCORAD	X	X	X	X	X	Section 8.2.5.
Itch NRS (current)		X				Section 8.2.6.1.1. Evaluated via eDiary on Day 1 at the following timepoints: before initial study cream application and 5, 15, 30, 45, and 60 minutes as well as 2, 4, and 6 hours post–study cream application. Note: Assessments at timepoints up to and including 60 minutes post–study cream application are required to be performed on-site. Assessments at all subsequent timepoints do not need to be completed at the clinic. The 6-hour assessment should be performed prior to the evening study cream application.
Itch NRS (24-hour recall)	eDiary is completed each evening from the screening visit through the last application of study cream during the VC period (night before Week 8 visit)					Section 8.2.6.1.
Skin Pain NRS (24-hour recall)	eDiary is completed each evening from the screening visit through the last application of study cream during the VC period (night before Week 8 visit)					Section 8.2.6.2.
Laboratory assessments						
Serum chemistry	X	X*	X		X	Section 8.3.4. *Only required if the interval between screening and Day 1 is > 2 weeks.
Hematology	X	X*	X		X	Section 8.3.4. *Only required if the interval between screening and Day 1 is > 2 weeks.
HIV antibody	X					Section 8.3.4.
FSH	X					Section 8.3.4. Women of nonchildbearing potential only

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

Visit (Range)	Screening	VC Period[a]				Notes
	Days −28 to −1 (+ 7 d)[b]	Day 1[c] (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8[d] or ET1 (± 3 d)	
Laboratory assessments (continued)						
Pregnancy testing	X	X	X	X	X	Section 8.3.4.1 and Section 5.1, Inclusion Criteria 11b. WOCBP should undergo a serum test at screening and a urine test at all subsequent scheduled visits. A positive urine test must be confirmed by a serum test.
[redacted]						

[a] Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed as clinically indicated (excluding tablet PRO questionnaires).
[b] For prior medications that require a 4-week washout period (see Section 5.2, Exclusion Criterion 5b), a 35-day screening period is allowed.
[c] Day 1 visit should be scheduled and conducted in the morning (AM). The current Itch eDiary assessments at timepoints up to and including 60 minutes post–study cream application are required to be performed on-site.
[d] Week 8 is the baseline for participants eligible to continue in the VCE period (BSA ≤ 20%).

Table 4: Schedule of Activities: Vehicle-Controlled Extension Period/Escape Arm

Visit (Range)	VCE Period[a]		Safety Follow-Up	Notes
	Weeks 12, 16, and 20 (± 7 d)	Week 24/EOT or ET2 (± 7 d)	30 Days (+ 7 d) After Week 24 or ET Visit	
Administrative procedures				
Contact IRT	X	X		Section 8.1.3.
Concomitant medications and procedures	X	X	X	Section 6.6.
Apply study cream at site under direct site staff supervision	X			Section 6.1.1. Only for participants with active AD lesions at time of visit.
Weigh/dispense study cream	X			Section 6.4. New tubes of study cream will be provided at each visit.
Collect/weigh returned study cream and review eDiary	X	X		Section 6.4.
Assess study cream compliance	X	X		Section 6.4.
Contact participant to confirm compliance with eDiary	X*			Section 6.4 and Section 8.1.4. *Telephone call contact should occur between regularly scheduled visits (eg, Weeks 10, 14, 18, and 22) to ensure compliance with the eDiary. AEs and concomitant medications can be recorded as well.
Safety assessments				
AE assessments	X	X	X	Section 8.3.1 and Section 9.
Targeted physical examination	X	X	X	Section 8.3.2.2. Conducted only when indicated by symptoms reported by the participant, AEs, or other findings; clinically significant abnormalities (in the investigator's judgment) are to be reported as AEs.
Comprehensive physical examination		X*		Section 8.3.2.1. *ET2 visit only.
Body weight	X	X	X	Section 8.3.3.
Vital signs	X	X	X	Section 8.3.3. To be taken before blood sampling and other procedures (not including PROs).

Table 4: Schedule of Activities: Vehicle-Controlled Extension Period/Escape Arm (Continued)

Visit (Range)	VCE Period[a]		Safety Follow-Up	Notes
	Weeks 12, 16, and 20 (± 7 d)	Week 24/EOT or ET2 (± 7 d)	30 Days (+ 7 d) After Week 24 or ET Visit	
PRO assessments				
DLQI	X	X	X	Section 8.2.6. All PROs must be completed before any other evaluations (except those necessary prior to registration of visits in the IRT) or study procedures on the day of the study visit and prior to discussions with the investigator or study site staff.
POEM	X	X	X	
EQ-5D-5L	X	X	X	
HADS	X	X	X	
WPAI-AD		X	X	
PROMIS Short Form - Sleep-Related Impairment (8a) (7-day recall)	X	X	X	
PROMIS Short Form - Sleep Disturbance (8b) (7-day recall)	X	X	X	
TSQM-9		X		
Efficacy assessments				
Evaluate %BSA affected by active AD	X	X	X	Section 8.2.2. Section 8.2.2.1. The presence of AD lesions in intertriginous regions should also be determined.
IGA	X	X	X	Section 8.2.3.
EASI	X	X	X	Section 8.2.4.
SCORAD	X	X	X	Section 8.2.5.
Itch NRS (7-day recall)	X	X	X	Section 8.2.6.1 and Section 8.2.6.2. Only captured during site visits, using 7-day recall; should be completed together with PROs listed above.
Skin Pain NRS (7-day recall)	X	X	X	
Laboratory assessments				
Serum chemistry	X*	X	X	Section 8.3.4. *Week 12 only.
Hematology	X*	X	X	Section 8.3.4. *Week 12 only.
Pregnancy testing	X	X	X	Section 8.3.4.1. A positive urine test must be confirmed by a serum test.

Table 4: Schedule of Activities: Vehicle-Controlled Extension Period/Escape Arm (Continued)

Visit (Range)	VCE Period[a]		Safety Follow-Up	Notes
	Weeks 12, 16, and 20 (± 7 d)	Week 24/EOT or ET2 (± 7 d)	30 Days (+ 7 d) After Week 24 or ET Visit	
Laboratory assessments (continued)				
[redacted]				

[a] Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed as clinically indicated (excluding tablet PRO questionnaires).

2. INTRODUCTION

2.1. Background

2.1.1. Ruxolitinib Cream

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate, and the 1.5% strength applied BID is approved in the US for the topical short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromized adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (OPZELURA 2023b). The approval in AD was based on data from 2 Phase 3 studies in adolescents and adults with mild to moderate AD (INCB 18424-303 and INCB 18424-304; Papp et al 2021, Papp et al 2023) and supported by the results of a Phase 2 study in adults with AD (INCB 18424-206; Kim et al 2020a, Kim et al 2020b). Refer to the IB for additional details on the nonclinical and clinical development.

More recently, ruxolitinib cream was approved in the US in JUL 2022 for the topical treatment of nonsegmental vitiligo (OPZELURA 2023b) and in the EU in APR 2023 for the treatment of nonsegmental vitiligo with facial involvement (OPZELURA 2023a) in adult and pediatric patients 12 years of age and older.

2.1.2. Atopic Dermatitis

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

Despite the availability of a number of treatment options, there is still a significant medical need for safe topical therapies that provide rapid and effective control of the signs and symptoms of AD. In the EU and US, the use of TCSs is recommended for the treatment of mild to moderate AD (Sidbury et al 2023, Wollenberg et al 2022a). Long-term treatment with TCSs is not recommended due to important side effects such as skin atrophy, telangiectasia, and striae distensae. For patients whose AD is not adequately controlled on, or who are intolerant to, or contraindicated to TCS, or where prolonged intermittent treatment with TCSs may be inappropriate (such as treating sensitive skin areas on the face and neck), TCIs such as tacrolimus and pimecrolimus are recommended. In addition, a PDE4 inhibitor, 2% crisaborole ointment, is approved in the US for patients 3 months and older with mild to moderate AD and has no such safety concerns or limitations but was shown to have modest efficacy (EUCRISA 2023). This product is no longer available in the EU (STAQUIS 2022). Therefore, for those patients who have an inadequate response with TCI treatment, or who are intolerant to TCIs, there is an unmet need for an alternative topical agent to treat their AD before it becomes severe enough to warrant the use of a systemic agent.

Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines known to promote the pathogenesis of AD. Ruxolitinib (INCB018424) is a potent and selective JAK1 and JAK2 inhibitor that is currently approved for use in tablet form for the treatment of patients with myelofibrosis and polycythemia vera in multiple countries and acute and chronic graft-versus-host disease in the EU (JAKAVI 2022) and US (Jakafi 2023). Recent studies suggest that JAK inhibition may have antipruritic effects by acting directly on sensory nerve fibers and may offer a novel therapeutic approach with dual anti-inflammatory and antipruritic properties (Reszke et al 2020, Steinhoff et al 2022).

2.2. Study Rationale

The use of TCSs and TCIs is recommended for the treatment of AD (Wollenberg et al 2022a). For those patients with AD that is not adequately controlled with TCSs and TCIs, or for whom those topical agents are not medically advisable, systemic treatments such as cyclosporine, the Th2-blocking biologics dupilumab and tralokinumab, and the oral JAK inhibitors baricitinib and upadacitinib are currently recommended (Wollenberg et al 2022b). However, these systemic agents require considerable monitoring for safety, special handling, or injection, so there is the need for a topical, nonsteroidal treatment in patients who do not respond to or tolerate current topical treatments.

Ruxolitinib cream has the potential to spare or delay the need for patients with AD to go on to these systemic agents. Subgroup analyses in the 2 previous Phase 3 studies (INCB 18424-303 and INCB 18424-304) showed ruxolitinib cream to be effective and safe in participants with moderate AD who would otherwise have been eligible for systemic therapies (Simpson et al 2021). In addition, these 2 Phase 3 studies did not have any specific entry requirements regarding prior AD therapies, yet ruxolitinib cream was shown to be effective and safe regardless of prior AD therapy, including in participants who had received prior therapy with TCSs and TCIs (Blauvelt et al 2021a). The current study has been designed to further evaluate the safety and efficacy of ruxolitinib cream in adults with moderate AD who had an inadequate response to, are intolerant to, or are contraindicated to both TCSs and TCIs and include participants who would otherwise have been eligible for systemic therapies.

2.2.1. Scientific Rationale for Study Design

Ruxolitinib 1.5% cream BID, which was shown to be safe and effective in Studies INCB 18424-303 and INCB 18424-304 and is the approved regimen in the US, will be assessed for safety and efficacy in this double-blind, multicenter, global study with 2 distinct VC periods (VC and VCE) and the option of an open-label escape arm. In the absence of a recommended third-line topical drug in Europe, the comparator in this study will be vehicle cream. Participants will be randomized 2:1 to the ruxolitinib 1.5% cream BID or vehicle cream BID group for the first 8 weeks of study. Coprimary and a key secondary efficacy endpoints will be assessed at Week 8, consistent with the previous Phase 3 studies. After completing 8 weeks of continuous treatment, all eligible participants with an adequate response, defined as achieving at least EASI50 from baseline, will continue on their blinded treatment allocation and will be evaluated during an additional 16-week VCE period for durability of response. Participants will be eligible to enter the ruxolitinib 1.5% cream open-label escape arm if EASI50 is not achieved at Week 8 or if an EASI50 response from baseline is lost during the VCE period.

During the VCE period, participants will only treat areas of the skin with active AD lesions (not to exceed 20% BSA). This upper limit of 20% BSA was originally based on practical considerations for patients who have to apply a cream twice a day, and to limit the potential for systemic ruxolitinib exposure. It has been used throughout the clinical development program of ruxolitinib cream in AD, including the Phase 3 studies INCB 18424-303 and -304, which showed that ruxolitinib cream was safe and well tolerated. If lesions clear, participants will stop treatment applications 3 days after they have disappeared. Participants will restart treatment of their AD at the first sign of recurrence. This as needed (reactive) use of study cream in the VCE period reflects the manner in which ruxolitinib cream is anticipated to be used in the outpatient, longer-term setting and mimics the treatment regimen used in the long-term safety period of Studies INCB 18424-303 and INCB 18424-304. The population to be studied matches that in the previous Phase 3 studies in terms of AD duration (≥ 2 years) but differs in that it focuses on adults (≥ 18 years) with moderate AD (defined as affecting 10%-20% BSA [excluding the scalp], an IGA score of 3, an EASI score > 7, and an Itch NRS score ≥ 4) with clear impact on quality of life at baseline (ie, DLQI score > 10) rather than adults and adolescents with mild to moderate AD. In addition, these participants must have a documented inadequate response, intolerance, or contraindication to TCSs and TCIs. These modifications from the population in Studies INCB 18424-303 and INCB 18424-304 will allow a focused evaluation of ruxolitinib cream in participants who have moderate AD after treatment with TCSs and TCIs. Enrollment will be stratified by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW or Europe).

The coprimary and secondary objectives and endpoints, which focus on assessing the efficacy, safety, and tolerability of ruxolitinib 1.5% cream BID, use assessments that are standard in AD studies such as EASI75, IGA-TS, and ITCH4 for efficacy and TEAEs, physical examinations, vital signs, and laboratory data for hematology and serum chemistry for safety and tolerability.

2.2.2. Justification for Dose

The ruxolitinib 1.5% cream BID regimen was demonstrated to be safe, effective, and well-tolerated in the 2 Phase 3 studies in participants with mild to moderate AD, leading to its approval by FDA, and hence this will be the regimen tested in this study in participants with moderate AD and compared with vehicle cream.

2.2.3. Brief Epidemiology of Disease Studied and Minority Populations

The prevalence and burden of AD varies widely both within and between countries inhabited by the same ethnic groups, which suggests strong environmental influences in disease expression, with socioeconomic status and affluence considered to be the main driving factors. Inequities in access to healthcare, and the quality of healthcare provided, among racial and ethnic minority groups are well-documented (Mosam and Todd 2023).

Within the US, there are well-documented differences in the incidence and prevalence of AD among certain racial and ethnic groups, especially in the pediatric population. In a pooled analysis of the National Survey of Children's Health 2003-2004 and 2005-2006, National Health Interview Survey 2008-2012, and National Health and Nutrition Examination Survey 2003-2004 and 2007-2008, African American/Black and multiracial/other children had 1.5- and 1.3-fold increased odds of having AD, respectively. Data on AD prevalence by race and ethnicity are more mixed among adults. For example, a meta-analysis using NHIS 2010, 2012 and NHANES

2003-2004 and 2005-2006 found that African American/Black, Hispanic, and Asian adults all had significantly lower odds of AD when compared with White adults. The disparity in prevalence reporting between children and adults may indicate that there are other factors at play, including potential under diagnosis of adult AD in patients who are non-White (Quan et al 2023).

2.3. Benefit/Risk Assessment

In the 2 Phase 3 AD studies in adolescents and adults, ruxolitinib 1.5% cream BID rapidly and effectively improved both the signs and symptoms of AD, being statistically significantly superior to vehicle cream BID at the end of the VC period (Week 8) for IGA-TS, EASI75, and ITCH4. The antipruritic effect of ruxolitinib 1.5% cream BID showed a rapid onset with evidence of a treatment effect on daily Itch NRS scores as early as Day 1 (ie, within 12 hours after the first application of study cream). The disease course (assessed by IGA scores and %BSA affected by AD at study visits during Weeks 8 through 52) was well controlled throughout the long-term extension period of the study. The treatment effects of ruxolitinib 1.5% cream BID on IGA-TS, EASI75, and Itch NRS scores and the long-term disease control of ruxolitinib 1.5% cream BID were consistently observed regardless of prior topical or systemic AD treatment (Blauvelt et al 2021a, Blauvelt et al 2021b) as well as in the subset of participants with more severe AD (Simpson et al 2021), suggesting the same might be true in this study.

Safety data from the 2 previous Phase 3 studies demonstrated that the use of ruxolitinib 1.5% cream BID continuously for 8 weeks followed by prolonged (44 weeks) intermittent use was safe and well tolerated. The TEAEs were generally Grade 1 or 2 in severity and were most often events of nasopharyngitis and upper respiratory tract infection. Frequencies of these events were low and within the expected range for the general AD population. Application site reactions were reported infrequently in participants who applied ruxolitinib cream; these events were mostly Grade 1 in severity, and the majority had resolved without interruptions or discontinuations of ruxolitinib cream treatment.

Overall, the benefit-risk profile of ruxolitinib 1.5% cream BID is expected to be positive when used in adults with moderate AD (defined as affecting 10%-20% BSA, an EASI score > 7, an IGA score of 3, an Itch NRS score ≥ 4, and a DLQI score > 10) who had an inadequate response to, are intolerant to, or are contraindicated to TCSs and TCIs. More detailed information about the known and expected benefits and risks and reasonably expected AEs of ruxolitinib may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Coprimary	
To establish the efficacy of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• Proportion of participants with EASI75 from baseline at Week 8. (EASI75 is defined as achieving ≥ 75% improvement in EASI score.) • Proportion of participants with IGA-TS at Week 8. (IGA-TS is defined as achieving an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline.)
Key Secondary	
To further assess the treatment effects of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• Proportion of participants with ITCH4 from baseline to Week 8. (ITCH4 is defined as achieving ≥ 4-point improvement in Itch NRS score.) • Proportion of participants with ITCH4 from baseline to Day 7. • Proportion of participants with ITCH4 from baseline to Day 3. • Proportion of participants with ITCH4 from baseline to Day 2.
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• The type, frequency, and severity of AEs as well as changes from baseline in vital signs and laboratory data for hematology and serum chemistry.
To further evaluate the efficacy of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• Proportion of participants with EASI75 from baseline at each postbaseline visit except Week 8. • Proportion of participants with IGA-TS from baseline at each postbaseline visit except Week 8. • Proportion of participants with ITCH4 from baseline at each postbaseline visit except Week 8. • Time to achieve ITCH4 during the VC period. • Time to achieve ITCH2 during the VC period. (ITCH2 is defined as achieving ≥ 2-point improvement from baseline in Itch NRS score.) • Change from baseline (pre–study cream application) in current Itch NRS score at 5, 15, 30, 45, and 60 minutes and 2, 4, and 6 hours post–initial dose on Day 1. • Proportion of participants achieving at least a 2-point decrease from baseline in current Itch NRS score at 5, 15, 30, 45, and 60 minutes and 2, 4, and 6 hours post–initial dose on Day 1.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
To further evaluate the efficacy of ruxolitinib cream in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs (continued).	• Proportion of participants achieving at least a 4-point decrease from baseline in current Itch NRS score at 5, 15, 30, 45, and 60 minutes and 2, 4, and 6 hours post–initial dose on Day 1. • Proportion of participants with EASI50 from baseline at each postbaseline visit. (EASI50 is defined as achieving ≥ 50% improvement in EASI score.) • Proportion of participants with EASI90 from baseline at each postbaseline visit. (EASI90 is defined as achieving ≥ 90% improvement in EASI score.) • Proportion of participants achieving both EASI75 from baseline and IGA-TS at each postbaseline visit. • Change from baseline at each postbaseline visit for the following: – AD-affected %BSA – EASI score – SCORAD score – Itch NRS score – Skin Pain NRS score • Time to open-label escape arm (defined as not achieving 50% improvement in EASI score from baseline at 2 consecutive visits at least 1 week apart) • Proportion of participants concurrently meeting all of the following criteria at each postbaseline visit: IGA score ≥ 3, EASI score ≥ 16, Itch NRS score ≥ 4, BSA ≥ 10%, and DLQI score > 10. • Time to concurrently meeting all of the following criteria: IGA score ≥ 3, EASI score ≥ 16, Itch NRS score ≥ 4, BSA ≥ 10%, and DLQI score > 10. • Proportion of participants who experience a relapse after study treatment discontinuation. (proportion of participants among EASI75 responders who are on study treatment at Week 24 who meet relapse criteria [loss of EASI50 from baseline] at the safety follow-up visit) • Time to first re-treatment during the VCE period. • Proportion of time off study treatment due to lesion clearance during the VCE period by visit. • Proportion of time on study treatment during the VCE period by visit.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
To evaluate quality of life and other PROs in participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs.	• Proportion of participants who achieve ≥ 4-point improvement in DLQI from baseline at each postbaseline visit. • Change from baseline in the following scores at each postbaseline visit: – DLQI – POEM – EQ-5D-5L – HADS – PROMIS Short Form – Sleep-Related Impairment (8a – 7-day recall) – PROMIS Short Form – Sleep Disturbance (8b – 7-day recall) • Change from baseline score at Weeks 8 and 24 in WPAI-AD.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3b, multicenter, randomized, double-blind, VC study with an extension period in adult (aged ≥ 18 years) participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs (see Figure 1). The study will be conducted at approximately 100 sites in North America, Asia-Pacific, and Europe.

For participants who meet all study inclusion criteria and none of the exclusion criteria, study cream will be assigned at the Day 1/baseline visit. Approximately 225 participants will be randomized 2:1 to blinded treatment with ruxolitinib 1.5% cream BID or vehicle cream BID, with stratification by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW or Europe).

During the 8-week VC period, participants will apply study cream BID to all areas identified for treatment at the Day 1/baseline visit even if the AD begins to improve and lesions decrease in size. If there are new areas to be treated (including expansion of existing areas or development of new areas), after consultation with the investigator, study cream should be applied to these areas in addition to the areas identified at the baseline visit (up to a maximum total of 20% BSA) for the remainder of the VC period. A study staff representative or designee will contact the participant at minimum 1 week prior to each clinic visit during the VC period to discuss eDiary compliance.

Efficacy will be evaluated during the VC period, including the proportion of participants achieving EASI75 and IGA-TS (coprimary endpoints), and ITCH4 at Week 8 as well as ITCH4 at Day 7, Day 3, and Day 2 (key secondary endpoints).

After completing 8 weeks of continuous treatment, all eligible participants with an adequate response, defined as achieving at least EASI50 from baseline, will continue blinded treatment allocation and will be evaluated during an additional 16-week VCE period for durability of response. Participants will be eligible to enter the ruxolitinib 1.5% cream open-label escape arm if EASI50 is not achieved at Week 8 or if an EASI50 response from baseline is lost during the VCE period (Note: < EASI50 must be observed at 2 consecutive visits, one of which can be an unscheduled visit, at least 1 week apart.)

Furthermore, investigators should consider alternative treatment options, such as systemic therapies, at or after completing the Week 8 visit, if any participant meets all of the following criteria (Note: prior to initiation, the investigator should discontinue study cream and the therapy escalation will be recorded in the eCRF):

- IGA score ≥ 3
- EASI score ≥ 16
- Itch NRS score ≥ 4
- BSA ≥ 10%

During the VCE period, participants (including those in the escape arm) will have study visits every 4 weeks for up to 24 weeks total. At each of these visits, including Week 8, the participant's AD lesions will be evaluated by the investigator to determine whether the

participant requires continuation of treatment or should (re)enter an observation/no treatment period. If the IGA score is ≥ 1, the participant will start or continue study cream BID. If the IGA score is 0 (clear), the participant will (re)enter an observation/no treatment period. Note: Participants should stop treatment application 3 days after the lesions have cleared.

Furthermore, during the VCE period (ie, starting at the Week 8 visit), participants will self-evaluate their AD symptoms between study visits and will treat areas of the skin (not to exceed 20% BSA) with active AD lesions only. If AD lesions clear at any time before the Week 24 visit, participants will stop treatment applications 3 days after the lesions have cleared and record the dates of these events in their eDiary. Participants who were in an observation/no treatment period will restart treatment at home at the first sign of recurrence and record the date of the new treatment. All treatment will be captured in the clinical database with the beginning and end dates as confirmed by the participant in the eDiary. A study staff representative or designee will contact the participant in between regularly scheduled clinic visits (eg, Weeks 10, 14, 18, and 22) to discuss eDiary compliance and to confirm the start and end date of treatment as applicable.

All participants will have a safety follow-up visit 30 days after their Week 24 or ET visit. An exception to this would be for participants who have been in an observation/no treatment period with an IGA score of 0 (clear) from Week 20 or earlier until Week 24; such participants could complete the safety follow-up and Week 24/EOT visits together. In practice, this would mean conducting all Week 24/EOT visit assessments plus the pregnancy test at the Week 24/EOT visit (see Section 8.9.1).

Participants will be assessed for the safety and tolerability of study cream throughout the study by monitoring the type, frequency, and severity of AEs; performing physical examinations; measuring vital signs; and conducting clinical laboratory assessments. Disease severity assessments, including PROs, will also be conducted.

4.2. Overall Study Duration

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

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study or the date that the last participant has discontinued study cream and has completed applicable safety follow-up assessments or is lost to follow-up.

In EU/EEA, the results of the study will be based on the date of the last visit of the last participant in the study globally to ensure the results are robust, meaningful, and representative of all multiregions by having complete follow-up data determined by the statistical hypotheses for the objectives established.

Estimated total duration of participation for an individual is up to approximately 34 weeks: 28 (+ 7) days in the screening period, 8 weeks in the VC period, 16 weeks in the VCE period, and 30 (+ 7) days in the safety follow-up period.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study site contract. The investigator is to notify the IRB/IEC of the study's completion or early termination in writing, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively or if required by a 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 the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in this Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

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

1. Adults aged ≥ 18 years at screening (Note: Legal adult age for Korea is ≥ 19 years).
2. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria.
3. AD duration of at least 2 years.
4. IGA score of 3 at screening and Day 1.
5. EASI score > 7 at screening and Day 1.
6. Itch NRS score ≥ 4 at Day 1, defined as the average of the 7 days directly before Day 1, with Itch NRS values available for at least 4 of the 7 days.
7. %BSA (excluding the scalp) with AD involvement of at least 10% and up to 20% at screening and Day 1.
8. DLQI score > 10 at screening and Day 1.
9. Documented recent history (within 12 months before the screening visit) of inadequate response, intolerance, or contraindication to TCSs and TCIs (see Section 6.6.1) as follows:
    a. Inadequate response:
        – For TCSs: Inability of a given TCS to induce and maintain remission or to contain the AD severity at an acceptable level (comparable to IGA score of 0 [clear] or 1 [almost clear]) despite treatment for 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for superpotent TCSs), whichever is shorter

            and

        – For TCIs: Inability of a given TCI to induce and maintain remission or to contain the AD severity at an acceptable level (comparable to IGA score of 0 [clear] or 1 [almost clear]) despite treatment according to the product prescribing information.

            Note: Documented (within 12 months before the screening visit) systemic treatment for AD (eg, oral corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) or phototherapy or photo(chemo)therapy can also be considered as a surrogate for inadequate response to TCSs and TCIs.

b. Intolerance: Clinically relevant side effects, safety risks, or skin tolerability issues that outweigh the potential treatment benefits and are the reason why a topical treatment could not be restarted or continued.

   Note: Documented history (more than 12 months prior to the screening visit) of clinically significant adverse reactions with use of TCSs and/or TCIs that in the opinion of the investigator outweigh the benefits of restarting treatment would also be considered as evidence of intolerance.

c. Contraindication: As defined in the product prescribing information.

10. Agree to discontinue all agents used to treat AD from screening through the final follow-up visit, except as outlined in Section 6.6.2 and Section 6.6.3.
11. Willingness to avoid pregnancy, breastfeeding, or fathering children based on the criteria below.
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of study cream and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy should be communicated to the participants and their understanding confirmed (see Appendix A).
    b. Female participants who are WOCBP must not be lactating or breastfeeding and have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first application of study cream on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last application of study cream and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Female participants not considered to be of childbearing potential are eligible (see Appendix A).
12. Ability to comprehend and willingness to sign an ICF. (Note: A signed written ICF must be obtained for inclusion; see Section 8.1.1.)

5.2. Exclusion Criteria

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

1. Unstable course of AD (spontaneously improving or rapidly deteriorating) as determined by the investigator in the 4 weeks prior to Day 1.
2. Concurrent conditions and history of other diseases as follows:
    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 Day 1.

c. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox) within 1 week before Day 1.
d. Any other concomitant skin disorder (eg, generalized erythroderma, such as Netherton syndrome), pigmentation, or extensive scarring that, in the opinion of the investigator, may interfere with the evaluation of AD lesions or compromise participant safety.
e. Presence of AD lesions only on the hands or feet without prior history of involvement of other classic areas of involvement such as the face or the flexural folds.
f. Other types of eczema within the 6 months prior to screening.

   Note: Seborrheic dermatitis on the scalp is allowed, as the scalp will not be treated with study cream.

g. Current or history of hepatitis B or C virus infection.

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

   a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction, or stroke within 6 months before Day 1; New York Heart Association Class III or IV congestive heart failure; or arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by the medical monitor/sponsor.
   b. History of malignancy in the 5 years preceding Day 1, except for adequately treated, nonmetastatic, nonmelanoma skin cancer.
   c. Current and/or history of arterial or venous thrombosis, including deep venous thrombosis and pulmonary embolism.
   d. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.
   e. History of severe anemia, severe thrombocytopenia, or severe neutropenia.

4. Any of the following clinical laboratory test results at screening:

   a. Hemoglobin < 10 g/dL
   b. Liver function tests:

      – AST or ALT ≥ 2 × ULN
      – Alkaline phosphatase > 1.5 × ULN
      – Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) with the exception of Gilbert's disease

   c. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation)
   d. Positive serology test results for HIV antibody
   e. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.

5. Use of any of the following treatments within the indicated washout period before Day 1:
    a. 5 half-lives or 12 weeks, whichever is longer: biologic agents. For biologic agents with washout periods longer than 12 weeks (eg, rituximab), consult the medical monitor.
    b. 4 weeks: systemic corticosteroids or adrenocorticotropic hormone analogs, cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive (eg, JAK inhibitors) or immunomodulating agents (eg, mycophenolate or tacrolimus).
    c. 2 weeks or 5 half-lives, whichever is longer - strong systemic CYP3A4 inhibitors.
    d. 2 weeks: immunizations with live-attenuated vaccines; sedating antihistamines unless on a long-term stable regimen (nonsedating antihistamines are permitted).

        Note: COVID-19 vaccination is allowed.

    e. 1 week: use of other topical treatments for AD, other than bland emollients (eg, Aveeno creams, ointments, sprays, soap substitutes), such as antipruritics (eg, doxepin cream), corticosteroids, calcineurin inhibitors, PDE4 inhibitors, coal tar (shampoo), antibiotics, or antibacterial cleansing body wash/soap.

        Note: Diluted sodium hypochlorite "bleach" baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
6. History of treatment failure with any systemic or topical JAK inhibitor (eg, ruxolitinib, tofacitinib, baricitinib, abrocitinib, upadacitinib) for AD or any other inflammatory condition.
7. Ultraviolet light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, sunlight or tanning booth) within 2 weeks prior to the baseline visit and/or intention to have such exposure during the study that is thought by the investigator to potentially impact the participant's AD.
8. 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.
9. 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.
10. Removed during Protocol Amendment 1. ~~Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before baseline with a strong cytochrome P450 3A4 inhibitor.~~
11. Known allergy or reaction to any component of the study cream formulation.
12. In the opinion of the investigator, are unable or unlikely to comply with the administration schedule, study evaluations, and procedures (eg, eDiary compliance).
13. 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, sponsor delegates (eg, contract research organizations), or investigator or are otherwise dependents of them.

15. The following participants are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection, or who are unable to express their consent per article L.1121-8 of the French Public Health Code, not affiliated to a social security per article L.1121-8-1 of the French Public Health Code.
16. In the EU, participants considered incapacitated (according to CTR Article 31).

5.3. Lifestyle Considerations

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

If sunscreen, makeup, or other cosmetics have been applied to the areas to be treated, participants should wash the treatment areas with mild soap and water and pat dry before application of study cream (see Section 6.6.2).

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

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

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent (if rescreened ≥ 28 days after the initial screening or ≥ 35 days after the initial screening for those participants on prior medications requiring a 4-week washout period, as described in Section 5.2, Exclusion Criterion 5b) and be assigned a new screening number. Reasons for screen failure will be recorded in the eCRF.

5.5. Recruitment Strategy and Retention of Participants

Potential study participants may be identified from the investigator's existing patient database, physician referrals, local or centralized advertisements, and direct-to-patient outreach (prescreener websites). Potential study participants may be presented with IRB/IEC-approved recruitment tools at the study site and advertisements (such as online social media platforms) before providing the written ICF. Any personal data gathered directly from respondents via prescreener websites will be collected based on affirmative participant acknowledgment of the relevant privacy policy and terms of use and affirmative participant consent (per GDPR 6.1.a) to the purpose of screening and study matching. Personal information records gathered under these

acknowledgments and consent are made available only to clinical study investigators (or other qualified staff at the clinical study site).

Following identification of a potential study participant, the investigator, delegated site staff, or referring physician will approach the potential participant and provide initial information relating to the clinical study. The investigator or their representative will follow the ICF process in Section 8.1.1 before performing any study-related procedures.

5.6. Replacement of Participants

Participants are not anticipated to be replaced during the study.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name	Ruxolitinib 1.5% cream	Vehicle
Dosage formulation	Cream	
Unit strength	1.5%	Not applicable
Route of administration	Topical	
Administration instructions	BID (morning and evening applications at least 1 hour before bedtime; optimally at equal intervals, ideally 12 hours apart, but with at least 8 hours between applications). On days of the study site visits, when the cream is applied under site staff supervision, the prior dose should be applied at least 4 hours before the visit. A thin film should be applied to all affected areas identified at baseline during the VC period and to active lesions only during the VCE period.	
Packaging and labeling	Study cream will be provided in 60-g tubes. Each tube will be labeled as required per country requirement.	
Storage	Ambient (15°C-30°C/59°F-86°F)	
Status of treatment in participating countries	Approved for AD in USA; investigational for AD in all other countries*	Not applicable

*Ruxolitinib 1.5% cream (15 mg/g 100-g tube) is approved by the EU for the treatment of nonsegmental vitiligo with facial involvement in adults and adolescents aged 12 years and older. Ruxolitinib cream does not have marketing authorization for the treatment of AD. The use of the investigational medicinal product (ruxolitinib cream) for AD is investigational and will not be in accordance with the terms of the EU marketing authorization for vitiligo.

Ruxolitinib or vehicle study cream will be supplied in 60-g tubes and applied topically as a thin film BID (optimally at equal intervals, ideally 12 hours apart but with at least 8 hours between applications, or at least 4 hours since the previous application on-site visit days when study

cream is applied under site staff supervision) to the affected areas in the morning and in the evening, with the evening application at least 1 hour before bedtime.

At the Day 1 baseline visit, an estimate of the %BSA to be treated will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. All AD areas identified at the baseline visit should continue to be treated through the end of the VC double-blind period (at Week 8), even if the area begins to improve or the AD resolves completely, unless the participant meets any criteria for stopping study cream.

If there are new areas to be treated, including expansion of existing areas or development of new areas, after consultation with the investigator, study cream should be applied to these areas in addition to the areas identified at the baseline visit (up to a maximum total of 20% BSA) for the remainder of the VC period, and the percentage of BSA to be treated will be recalculated and increased accordingly. This new estimate will be entered into the IRT system to calculate the number of tubes of study cream to be dispensed. During the VC period, participants whose additional new areas to be treated in addition to the areas identified at the baseline visit exceed 20% BSA will be discontinued from study treatment and complete the ET visit.

The VCE period starts at the Week 8 visit and completes at the Week 24 visit, with the final possible application being the evening application on the day before the Week 24 visit. During the VCE period, only areas with active disease should be treated.

After completing 8 weeks of continuous treatment, all eligible participants with an adequate response, defined as achieving at least EASI50 from baseline, will continue their blinded treatment allocation and will be evaluated during an additional 16-week VCE period for durability of response. Participants will be eligible to enter the ruxolitinib 1.5% cream open-label escape arm if EASI50 is not achieved at Week 8 or if an EASI50 response from baseline is lost during the VCE period. (Note: < EASI50 must be observed at 2 consecutive visits, one of which can be an unscheduled visit, at least 1 week apart.)

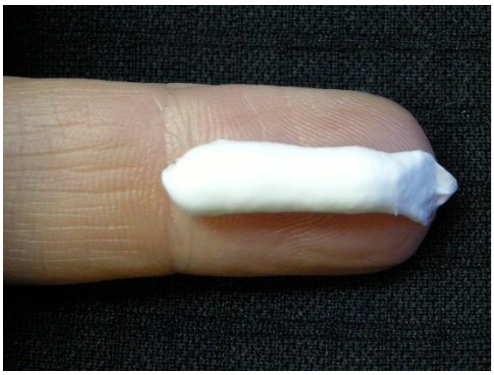
The start and end dates of treatment applications will be captured by the participant. Once the lesions clear (IGA score of 0), participants should continue to apply study cream for an additional 3 days to the areas of the body where lesions were last present before discontinuing treatment. Following clearance, if a lesion recurs, treatment should be resumed at the first sign of recurrence.

At any time during the VCE period, if a participant's total AD-affected area exceeds 20% BSA, the participant will be discontinued from study treatment and complete the ET visit.

6.1.1. Study Treatment Application Guidance

Participants should remove study cream from the tube and apply the study cream with their fingertip (see Figure 2) in small amounts until all of the areas to be treated are covered by a thin, even film. Additional training will be provided in the SRM.

Figure 2: Study Cream Application Using a Fingertip



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

In the clinic, the amount of study cream used will be determined by weighing a tube before and after the participant applies a thin film of study cream to the affected areas. New tubes of study cream will be provided at each visit.

Study cream should be applied in front of site staff for all on-site visits. The Day 1 baseline visit should be performed in the morning (AM). The study personnel need to ensure that they understand the quantity to be used and the application method. For all other (non-Day 1) visits, the participant should apply either of the 2 daily doses at the site, as long as the previous dose was applied at least 4 hours prior (see Section 8.4).

Study cream application does not apply to the Week 8 visit if the IGA score is 0 or to the Week 24 or ET visits.

Application instructions will be provided by the site study staff, and the participants will record their daily applications plus any missed or interrupted doses via an eDiary. Participants must not apply study cream more or less often than BID. Refer to the SRM for participant instructions for handling study cream.

6.2. Preparation, Handling, and Accountability

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

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

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

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

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

The investigational product must be used only in accordance with the Protocol (see Section 6.1). The investigator or designee will also maintain records adequately documenting that the participants were provided the specified study cream. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study cream until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee the destruction of any remaining study cream according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study cream back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study cream is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system. The system will assign study treatment in a 2:1 ratio, stratified by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW vs Europe), assign the participant study number, track participant visits, randomize according to the defined parameters, maintain the blinding, and manage study cream inventory. Full details will be provided in the IRT Manual. Study treatment will be dispensed at the study visits (see Table 3 and Table 4).

At screening, participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the

participant's assignment to 1 of the 2 treatment groups in the study, according to the randomization schedule generated before the study by the sponsor's unblinded statistician and provided to IRT vendor. Each participant will be dispensed blinded study cream labeled with their unique randomization number throughout the study.

Participants and investigators will remain blinded to each participant's treatment assignment throughout the study; however, the sponsor will be unblinded after the primary database lock (see Section 10.6). Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.7).

Matching vehicle cream contains the same excipients as the active drug product, the only difference is the replacement of the active component. Hence, the use of vehicle cream maintains the blind for participants.

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

Qualified clinical staff will review the eDiary entries for compliance at study visits. Furthermore, the study staff should contact the participant at minimum 1 week prior to each visit during the VC period (see Table 3) and in between regularly scheduled visits during the VCE period (see Table 4) to confirm the participant's compliance with completion of the eDiary. Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the prescribed number of applications during participation in the VC and VCE periods of the study. Participants who are noncompliant during the VC period or the VCE period (if on treatment) will be reinstructed by the investigator (or designee), and the sponsor should be consulted by the investigator for instruction on the proper handling of the participant.

Drug accountability will be assessed by documenting the quantities of study cream used between study visits (tube counts and weighing). At the first clinic visit and subsequent study visits, the amount of study cream applied is to be determined by weighing a tube before and after the participant applies a thin film of study cream to the affected areas. Participants will be instructed to bring all assigned/dispensed study cream with them to the study visits (this includes empty tubes) in order for site personnel to assess study cream accountability. Participants will be instructed to not discard/throw away any empty/used tubes.

6.5. Dose Modifications

There are no application adjustments/modifications allowed (decrease or increase in study cream strength or frequency of application) except for study cream interruption or permanent discontinuation if needed (eg, for management of an AE; see Section 6.5.1 and Section 6.5.2).

Temporary study cream interruption due to an AE could occur at any time during the study periods; however, temporary study cream interruption due to clearance of the AD lesions is only allowed during the VCE period (see Section 4.1 and Section 6.1).

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

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

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

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

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

Table 7: Guidelines for Interruption and Restarting of Study Cream Due to Laboratory Abnormalities

Adverse Event	Action Taken
Any Grade 3 laboratory abnormality (with the exception of asymptomatic elevations in triglyceride, cholesterol, or amylase)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Interrupt study cream, based on clinical judgment in consultation with the medical monitor (whenever possible), taking into account the relatedness of the AE to the study cream and the participant's underlying condition. • Interruption may occur after the initial test result or may be delayed until or unless the repeat test confirms the laboratory abnormality; however, if the repeat test does confirm the laboratory abnormality, the study cream must be interrupted unless the medical monitor approves continuation. • At the discretion of the investigator, after consultation with the medical monitor, study cream application may be restarted once the AE has resolved.
Any Grade 4 laboratory abnormality	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Interruption may occur after the initial test result. • Permanently discontinue study cream if laboratory abnormalities are confirmed and they are considered related to study cream. Study cream may also be discontinued after the initial laboratory abnormality, with approval from the medical monitor.

6.5.2. Criteria for Permanent Discontinuation of Study Cream

Participants must permanently discontinue study cream if they meet any of the following criteria:

- Occurrence of an AE that is related to treatment with the study cream that, in the judgment of the investigator or the medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Worsening of AD that requires treatment with a prohibited concomitant medication
- Any Grade 4 laboratory abnormality (see Table 7) considered related to the study cream
- Persistent AE requiring an interruption of study cream for more than 2 weeks without resolution of the AE

See Section 7 for discontinuation procedures.

6.6. Prior and Concomitant Medications and Procedures

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

Concomitant medications administered beyond 30 days after the last application of study cream should only be recorded for SAEs. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Prior Therapies for Treatment of Atopic Dermatitis

Acceptable documentation of recent history with TCSs and TCIs or, when appropriate, systemic treatments must be collected by the investigator or a qualified designee at the screening visit and must include treatment details (eg, name, start/end dates, regimen) and treatment outcome (eg, inadequate response, intolerance). For instances in which a topical agent was not restarted due to prior intolerance (see Section 5.1, Inclusion Criterion 9), the reason for not restarting must also be recorded on the eCRF. The necessary information can be collected from one or more of the following sources and must be recorded and signed off in an investigator attestation:

- Communication with the participant's treating physician
- Documentation at the investigative site, such as the following:
  - Medical history records
  - Pharmacy records (with clearly listed dates of dispensation)
  - Hospital records
  - Participant interview

6.6.2. Permitted Medications and Procedures

The following are permitted during the study:

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

  Note: Emollients should not be used within 4 hours before and 2 hours after application of study cream.

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

6.6.3. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Short-term use of systemic corticosteroids may be permitted to treat acute AEs (eg, asthma) during the VCE period, and the decision to keep the participant in the study (or to permanently discontinue study cream) will be made in consultation with the medical monitor and sponsor.
- Participants may continue using sedating antihistaminic drugs, as long as their use is part of a pre-existing, well-established, and stable treatment regimen, 2 weeks prior to Day 1 and throughout the first 8 weeks of study. There are no restrictions for use of nonsedating antihistamines.
- Use of any over-the-counter, nonprescription preparations deemed acceptable by the investigator is permitted under an established and stable treatment regimen 2 weeks prior to Day 1 and throughout the first 8 weeks of the study.
- Use of any prescription medication (including phytotherapeutic, herbal, or plant-derived preparations) within 2 weeks before Day 1 through the safety follow-up visit is allowed if deemed acceptable by the investigator.
- Immunizations with a live-attenuated vaccine are not recommended during the VC and VCE periods unless deemed necessary by the investigator.
- Allergen immunotherapy (desensitization) that is ongoing at a stable dose at the time of study entry may be continued while on study but only at the same dose throughout the first 8 weeks of the study.
- Bleach baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the first 8 weeks of the study.
- Topical anti-infectives or other topical treatments applied to active AD lesions should not be used for at least 4 hours before and 2 hours after application of study cream.

6.6.4. Prohibited Medications and Procedures

The following are not permitted during screening or the VC/VCE periods:

- Any investigational medication other than the study cream
- Any of the following topical treatments: corticosteroids, calcineurin inhibitors, PDE4 inhibitors, or aryl hydrocarbon receptor–modulating agents
- Other topical agents for treatment of AD (except bland emollients as noted in Section 6.6.2)
- Treatment known to affect the course of AD
- Systemic corticosteroids, methotrexate, cyclosporin A, azathioprine, biologic therapies, or other immunosuppressant agents
- Phototherapy or tanning beds
- Strong systemic CYP3A4 inhibitors

6.7. Treatment After the End of the Study

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Lack of efficacy response during the VCE period (defined as no change/improvement in %BSA, IGA score, or EASI score when treated with ruxolitinib cream in the escape arm continuously for 8 weeks).
- AD worsens during either the VC period or the VCE period (including the escape arm), to the point where the extent of AD to be treated (ie, all areas excluding the scalp) exceeds 20% BSA.
- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety monitoring.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Any AE of unacceptable severity as noted in Section 6.5.2.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- Participants who are noncompliant with study cream (see Section 6.4) or who use more than one 60-g tube per 4 days will have the application instructions reinforced by the investigator or a qualified designee. Participants who after 2 consecutive study visits and reinforcement of study cream application instructions by site staff again fail to meet compliance benchmarks or again use more than one 60-g tube per 4 days may be considered for withdrawal from the study. The medical monitor should be consulted for instruction on handling the participant.
- If, during the course of the study, a participant is found not to have met eligibility criteria, the sponsor's medical monitor or delegate, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures (eg, completion of eDiary), the sponsor's medical monitor (or designee) should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment prior to the Week 24/EOT study visit, an ET visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. The date of the last application of study cream and the reason for discontinuation of study cream will be recorded in the eCRF.

If a participant is discontinued from study treatment:

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

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

7.2. Participant Withdrawal From the Study

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

Note: A participant may withdraw from the study without having to provide their reason(s) for withdrawing prematurely and without penalty or loss of benefits to which the participant is otherwise entitled.

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

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 they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted.
  - Informed consent must be obtained using the most current IRB/IEC-approved version in a language that is native and understandable to the participant. An ICF template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template, and all site-specific changes must be approved by the IRB/IEC and the sponsor or its designee. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center. Note: For EU countries, participants who are considered incapacitated (according to CTR Article 31) are not allowed to participate in this clinical study.

- The participant must be informed that their personal data collected for the study will be used in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF (if rescreened > 28 days after the initial screening [or > 35 days for participants on prior medications requiring a 4-week washout period as described in Section 5.2, Exclusion Criterion 5b]) and must be assigned a new participant number.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Day 1). Informed consent must be obtained before performing any study-specific procedures. Screening assessments for determination of eligibility may be performed over a period of up to 28 days (or up to 35 days for participants on prior medications requiring a 4-week washout period as described in Section 5.2, Exclusion Criterion 5b). Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

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

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the country's abbreviation, the site ID, and the participant number. Site staff should contact the IRT 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 treatment assignment. Additionally, the IRT system will be contacted at each regular study visit during both the VC period and the VCE period as indicated in Table 3

and Table 4 to update the study cream supply. The IRT system will also be used during unscheduled visits to adjust the amount of study cream to be dispensed if the participant's %BSA of AD lesions to be treated has increased (during the VC period) or has either increased or decreased (during the VCE period). Furthermore, the IRT system will be used during scheduled or unscheduled visits upon entry into the escape arm and the amount of open-label ruxolitinib 1.5% cream to be dispensed will be adjusted based on participant's %BSA of AD lesions to be treated. Additional details are provided in the IRT Manual.

8.1.4. eDiary and Reminder Cards

A study-specific eDiary will be issued, via a handheld device, to each participant at the screening visit. Itch NRS (24-hour recall) and Skin Pain NRS (24-hour recall) information will be entered in the eDiary in the evening, and dose administration details will be entered in the morning and evening (see Table 3 and Table 4).

The investigator will ensure that participants are properly trained on the use of the eDiary and the importance of completing assessments as scheduled. Participants are required to complete the training module on the device at the site, and site staff must verify completion.

The investigator or site designee will be responsible for monitoring participant compliance with the eDiary and follow-up where necessary to minimize missing data. Qualified site staff will review the participants' entire eDiary entries for completeness and compliance with training and directions for PROs as outlined in Section 8.2.6 during each of the study visits and on a regular basis between visits. Furthermore, the study staff should contact the participant at minimum 1 week prior to each visit during the VC period (see Table 3) and in between regularly scheduled visits during the VCE period (see Table 4) to confirm the participant's compliance with completion of the eDiary.

During the VC and VCE periods, dose administration information is to be entered for 2 timepoints a day to match the BID schedule. The dose administration information to be entered will reflect whether the study cream was applied or not at that timepoint, and if not applied whether it was part of a formal dose interruption (eg, for lesion clearance or an AE) or because the dose was accidentally missed. Daily Itch NRS (24-hour recall) and Skin Pain NRS (24-hour recall) scores are to be entered every day during the VC period. During the VCE period, Itch NRS (7-day recall) and Skin Pain NRS (7-day recall) scores are to be entered via tablet during site visits.

Participants who continue in the VCE period will continue to complete the eDiary, which will be collected at the Week 24/EOT visit.

Participants will be provided with a reminder starting on Day 1 and at all VC and VCE visits through Week 24. The reminder will indicate the date and time of the next visit and will also remind the participant that one of the 2 daily applications of study cream will take place at the clinic under site supervision after blood collection for PK (see Section 8.4) 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 treatments within the past 2 years that are considered to be clinically significant by the investigator.

As race and/or ethnicity data are not to be analyzed from a scientific or medical perspective, but rather are to be reported in a descriptive format only in the CSR, data on race and/or ethnicity from France must not be collected as per GDPR and local data protection law and requirements.

8.1.5.2. Disease Characteristics and Treatment History

Relevant AD-targeted medical history 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 surgical or other procedures, will be recorded in the eCRF. Medical history of other conditions related to AD will be collected as well. Information about previous AD treatment history (within 12 months prior to screening) and their outcomes will be collected (see Section 5.1, Inclusion Criteria 9, and Section 6.6.1).

8.2. Efficacy Assessments

8.2.1. Health Economics

Health economic data will be assessed through the DLQI (see Section 8.2.6.3), PROMIS Sleep Questionnaires (see Section 8.2.6.7), HADS (see Section 8.2.6.8), WPAI-AD (see Section 8.2.6.6), and EQ-5D-5L (see Section 8.2.6.5).

8.2.2. Body Surface Area

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

Participants must have BSA involvement (excluding the scalp) of at least 10% and no more than 20% at the screening and baseline visits for the VC period to enroll in the study; they may have 0% to 20% BSA involvement at Week 8 to continue into the VCE period.

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

8.2.2.1. Characterization of Atopic Dermatitis Involvement in Intertriginous Regions

The presence of AD lesions in the intertriginous regions (ie, axillae, anogenital area, inframammary folds, and infra-abdominal folds) will be determined at each visit and documented in the eCRF (see Table 3 and Table 4).

8.2.3. Investigator's Global Assessment

Investigator's Global Assessment is an overall eczema severity rating on a 0 to 4 scale that will be assessed during site visits (see Table 3 and Table 4). The severity 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: FDA 2022.

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

Participants must have an IGA score of 3 at the screening and baseline visits to enroll in the study; they may have an IGA score of 0 to 4 at Week 8 to continue into the VCE period.

During the VCE period, including Week 8, IGA scores will be evaluated by the investigator to determine whether the participant requires continuation of treatment or should (re)enter an observation/no treatment period. If the IGA score is ≥ 1, the participant will start or continue study cream BID. If the IGA score is 0 (clear), the participant will (re)enter an observation/no treatment period.

8.2.4. Eczema Area and Severity Index

Atopic dermatitis will be assessed as outlined in the SoA (see Table 3 and Table 4) using the EASI scoring system, which is a validated scoring system that grades the physical signs of AD to provide a measure of AD severity (ranging from 0 to 72) (Hanifin et al 2001). The EASI scoring system examines 4 regions of the body (head/neck, upper limbs, trunk, and lower limbs) and weights them. Each of the 4 body regions is assessed separately for erythema (E), induration/papulation/edema (I), excoriations (Ex), and lichenification (L) for an average degree of severity of each sign in each region. Refer to the SRM for the EASI calculation guides.

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

8.2.5. SCORing Atopic Dermatitis

The SCORAD (refer to the SRM) is a tool to assess the extent and severity (ie, intensity) of eczema and will be completed before, during, and after treatment to determine whether the treatment has been effective (Oakley 2009). This will be performed during all VC and VCE period study visits starting at baseline (see Table 3 and Table 4).

- 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. The intensity of redness, swelling, oozing/crusting, scratch marks, skin thickening (lichenification), dryness (this is assessed in an area where there is no inflammation) is assessed individually 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 analog 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) for the participant and will be calculated as follows: A/5 + 7B/2 + C.

8.2.6. Patient-Reported Outcome Assessments

Patient-reported outcomes (including quality of life and itch) will be assessed using the following tools via a tablet at the site: DLQI, POEM, EQ-5D-5L, Itch NRS (7-day recall during the VCE period), Skin Pain NRS (7-day recall during the VCE period), PROMIS Short Form – Sleep-Related Impairment (8a), PROMIS Short Form – Sleep Disturbance (8b), HADS, WPAI-AD, and TSQM-9. The eDiary will also be utilized during the VC period for the Itch NRS (current and 24-hour recall) and Skin Pain NRS (24-hour recall). All PRO assessments (via tablet at the site; note this does not apply to the eDiary PROs) should be completed before other evaluations or study procedures (except those necessary prior to registration of visits in the IRT) in order to avoid bias in the participants' responses to the questionnaires.

For the daily Itch NRS (24-hour recall; see Section 8.2.6.1) and daily Skin Pain NRS (24 hour recall; see Section 8.2.6.2) assessments during the VC period, participants will use a handheld device (eDiary). The participant will be instructed to complete the eDiary during specific timepoints needed for each assessment beginning on the day of screening through the evening before the Week 8 visit or treatment discontinuation.

At the baseline (Day 1) visit, Itch NRS (current) assessments will also be collected in the eDiary at the prespecified timepoints (ie, before initial study cream application and 5, 15, 30, 45, and 60 minutes as well as 2, 4, and 6 hours post–study cream application).

The questionnaires will be distributed at the time of consent and assessed as follows:

- Assessments completed daily at home in the evening via eDiary during screening and for the duration of the VC period:
  - Itch NRS 24-hour recall (see Section 8.2.6.1)
  - Skin Pain NRS 24-hour recall (see Section 8.2.6.2)
- Assessments completed only on Day 1 initiated at the site and finalized at home via eDiary
  - Itch NRS current (see Section 8.2.6.1.1)
- Assessments completed at study site visits via tablet as per Table 3 and Table 4:
  - Itch NRS (7-day recall [VCE period]; see Table 4; see Section 8.2.6.1)
  - Skin Pain (7-day recall [VCE period]; see Table 4; see Section 8.2.6.2)
  - DLQI (7-day recall; see Section 8.2.6.3)
  - POEM (7-day recall; see Section 8.2.6.4)
  - EQ-5D-5L (current day; see Section 8.2.6.5)
  - WPAI-AD (7-day recall; see Section 8.2.6.6)
  - PROMIS Short Form – Sleep-Related Impairment (8a) (7-day recall; see Section 8.2.6.7.1)
  - PROMIS Short Form – Sleep Disturbance (8b) (7-day recall; see Section 8.2.6.7.2)
  - HADS (7-day recall, see Section 8.2.6.8)
  - TSQM-9 (see Section 8.2.6.9)

8.2.6.1. Itch Numeric Rating Scale

The Itch NRS is a daily participant-reported measure (24-hour or 7-day recall) of the worst level of itch intensity (refer to the SRM; Silverberg et al 2021). Participants will be asked to rate the itch severity of their AD by selecting a number from 0 (no itch) to 10 (worst itch imaginable) that best describes their worst level of itching in the past 24 hours via the eDiary as outlined in the SoA during the VC period (see Table 3) and in the past 7 days via the tablet during Protocol-defined clinic visits during the VCE period (see Table 4).

Participants will use an eDiary, on a device issued to them (see Section 8.1.4), to record itch severity. The participants will be instructed to complete the eDiary each evening beginning on the day of screening through the last application of study cream during the VC period (night before Week 8 visit). This is particularly important for the 7 days immediately prior to the Day 1/baseline, Week 2, Week 4, and Week 8 visits, as Itch NRS scores are required for at least

4 of those 7 days during each of these 4 timepoints to allow evaluation of participant eligibility and the Itch NRS endpoints.

8.2.6.1.1. Current Itch Numeric Rating Scale

On the morning of Day 1 (if the participant qualifies for randomization into the study) visit only, participants will be asked to evaluate the current intensity of their itch at the following assessment times: directly before initial study cream application and 5, 15, 30, 45, and 60 minutes as well as 2, 4, and 6 hours post–study cream application. The 6-hour assessment should be performed prior to the evening study cream application. All assessments at timepoints up to and including 60 minutes post–study cream application will be conducted during the clinic visit under supervision of site personnel. Assessments at all subsequent timepoints do not need to be completed at the clinic. Participants will be asked to rate the current itch severity of their AD by selecting a number from on a scale from 0 to 10, with 0 indicating no itch and 10 indicating the worst itch imaginable (Phan et al 2012, Verweyen et al 2019, Yosipovitch et al 2019). The current Itch NRS was modified from the 7-day Itch NRS and is presented in the SRM.

8.2.6.2. Skin Pain Numeric Rating Scale

The Skin Pain NRS is a daily participant-reported measure (24-hour or 7-day recall) of the worst level of pain intensity from 0 (no pain) to 10 (worst pain imaginable; Silverberg et al 2021). Participants will be asked to rate the pain intensity by selecting a number that best describes the worst level of pain in the past 24 hours via the eDiary during the VC period (see Table 3) and in the past 7 days via tablet at the site during the VCE period (see Table 4).

Participants will be issued an eDiary in which to record skin pain severity. The participants will be instructed to complete the eDiary each evening beginning on the day of screening through the last application of study cream during the VC period (night before Week 8 visit; see Table 3) and on a tablet at the site during scheduled VCE period study visits (see Table 4). Detailed directions for the administration of a diary will be provided in the SRM.

8.2.6.3. Dermatology Life Quality Index

The DLQI is a simple, 10-question validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days (see Table 3 and Table 4; refer to the SRM; Finlay and Khan 1994).

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)

8.2.6.4. Patient-Oriented Eczema Measure

The POEM (refer to the SRM) is to be completed using 7-day recall via tablet at each visit starting at the baseline visit during the VC period and at select visits during the VCE period (see Table 3 and Table 4).

The POEM is a 7-question quality-of-life assessment used for monitoring atopic eczema severity, focusing on the illness as experienced by the participant. The questionnaire asks how many days the participant has been bothered by various aspects of their skin condition during the past week. The response options and corresponding scoring questionnaires are no days (0), 1 to 2 days (1), 3 to 4 days (2), 5 to 6 days (3), and every day (4), with a range in score of 0 to 28 (Charman et al 2004).

8.2.6.5. EQ-5D-5L

The EQ-5D (refer to the SRM) is a validated, self-administered, generic utility questionnaire wherein participants 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 baseline) and at specific VCE visits, as outlined in the SoA (see Table 3 and Table 4), the participant will be asked (via tablet) to indicate their health state today 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).

8.2.6.6. Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis

The WPAI-AD questionnaire (refer to the SRM) is a validated 6-item instrument, completed (via tablet; see Table 3 and Table 4), 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).

8.2.6.7. PROMIS Sleep Questionnaires

The PROMIS 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 will be completed (via tablet) with a 7-day recall during the VC and VCE periods (see Table 3 and Table 4). Refer to the SRM for detailed instructions.

8.2.6.7.1. PROMIS Short Form – Sleep-Related Impairment (8a)

The PROMIS Short Form – Sleep-Related Impairment (8a) questionnaire 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 their sleep impairment. The recall period will be the past 7 days for both the VC and VCE periods.

8.2.6.7.2. PROMIS Short Form – Sleep Disturbance (8b)

The PROMIS Short Form – Sleep Disturbance (8b) questionnaire 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 a 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 7 days for both the VC and VCE periods.

8.2.6.8. Hospital Anxiety and Depression Scale

The HADS is a 14-item questionnaire to be completed by tablet; the questionnaire assesses the levels of anxiety and depression a person is currently experiencing (Zigmond and Snaith 1983; see Table 3 and Table 4). There are 7 questions each for measuring anxiety and for measuring depression, with 4 possible responses to each question (responses are scored as 0, 1, 2, or 3). Separate scores are calculated for anxiety and depression. The recall period will be the past 7 days for both the VC and VCE periods. Refer to the SRM for detailed instructions.

8.2.6.9. Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication

Participants will be asked to complete the TSQM-9 questionnaire via tablet (see Table 3 and Table 4). The TSQM-9 is a 9-item measure that assesses the most common dimensions participants use to evaluate their medication (ie, global satisfaction, effectiveness, and convenience; Bharmal et al 2009). The results for each scale are presented from 0 to 100, where higher scores represent better satisfaction. Refer to the SRM for detailed instructions.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in Table 3 and Table 4.

Guidelines regarding the management of relevant laboratory or other safety assessment abnormalities are provided in Section 6.5.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last application of study cream. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study cream. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs)

should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

All SAEs will be reported to the sponsor or designee by the investigator immediately without undue delay and not later than 24 hours of obtaining knowledge of the events. The investigator will also submit any updated SAE data to the sponsor immediately without undue delay and not later than 24 hours of obtaining knowledge of the update.

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

8.3.2. Physical Examinations

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

8.3.2.1. Comprehensive Physical Examination

At the screening visit and Week 24 or ET visit as indicated in Table 3 and Table 4, a comprehensive physical examination should be conducted and documented in the eCRF. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

8.3.2.2. Targeted Physical Examination

At visits indicated in Table 3 and Table 4, a targeted physical examination will be a symptom-directed evaluation (ie, conducted only if indicated by symptoms, AEs, or other findings); clinically significant abnormalities (in the investigator's judgment) are to be reported as AEs and documented on the Adverse Events Form in the eCRF.

8.3.3. Vital Signs, Height, and Weight

Vital signs, height, and weight will be measured as outlined in Table 3 and Table 4. Vital signs are taken before blood sampling and other procedures (not including all PROs).

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

8.3.4. Laboratory Assessments

All Protocol-required clinical laboratory assessments (see Appendix B) must be conducted in accordance with the Laboratory Manual and Table 3 and Table 4. Day 1 testing will be performed only if the interval between this visit and screening is > 2 weeks. A central laboratory will perform all clinical laboratory assessments for safety (blood chemistry and hematology assessments) and will store the samples for PK and pharmacodynamic analysis. Additional testing may be required by the sponsor based on emerging safety data. Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

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

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

8.3.4.1. Pregnancy Testing

A urine pregnancy test will be required for all female participants who have reached menarche. The urine pregnancy test will be performed locally as outlined in Table 3 and Table 4, and as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected) or per country-specific requirement. 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 treatment and continue participation in the study.

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

8.3.4.2. Serology

An HIV assessment will be performed at the screening visit to rule out HIV infection (see Appendix B). Serology tests should be performed early in the screening process due to the length of time needed to obtain the results. If a participant tests positive for HIV, the investigator will be responsible for patient management per local and country requirements (eg, referring the participant to their general practitioner or other appropriate services). Additional tests may be performed if clinically indicated.

8.6. Storage and Future Use of Biological Samples

The biological samples to be collected from participants in this study include blood (laboratory, PK, and biomarker). The samples will be used only for the purposes described in this Protocol. Anonymized participant samples will be transported to the sponsor or designated vendor for analysis as detailed in the vendor-specific study manual. All laboratory samples will be destroyed immediately following analysis. Pharmacokinetic samples will be destroyed after the final bioanalysis report or CSR. Biomarker samples will be stored for up to 10 years from the first CSR for study-related research.

8.7. Unscheduled Visits

Unscheduled study visits may occur at any time medically warranted, including when participants develop new areas of AD. Any appropriate clinical and laboratory tests may be performed as clinically indicated. Any assessments performed at those visits should be recorded in the eCRF.

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

8.8. End of Treatment and/or Early Termination

The EOT visit coincides with the Week 24 visit. A participant who completes the Week 24/EOT visit will have reached the end of treatment with study cream.

If a decision is made that the participant will permanently discontinue study cream prior to the Week 24/EOT visit, then the ET visit should be conducted. If the ET visit coincides with a regular study visit, then the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET pages in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the ET procedures completed.

8.9. Follow-Up

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the Week 24/EOT or ET visit and the scheduled follow-up visit, which should occur 30 days after the Week 24/EOT or ET visit, with the following 2 exceptions:

- The follow-up visit should occur at the Week 24/EOT visit for participants who have been in an observation/no treatment period with an IGA score of 0 (clear) from Week 20 or earlier until Week 24.
- The follow-up visit should occur 30 days after the last application of study cream if the Week 24/EOT or ET visit was not performed.

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

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study cream.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, electrocardiogram, 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 disease progression) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study cream administration are to be reported as an AE. • New signs and/or symptoms due to the study disease that develop after the first dose of study cream are to be captured on the appropriate efficacy CRF. Any worsening of the underlying disease that is more severe than expected for the participant's condition is to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dose administration errors of a study cream (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases, pre-existing conditions, or new conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

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

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

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

Adverse Event and Serious Adverse Event Recording

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study cream and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB for study cream in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study cream administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- Once an AE is detected, it should be followed in the Adverse Events Form in the eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study cream, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance via the SAE EDC CRF until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) immediately without undue delay but not later than 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study cream or study procedure[s]), all SAEs occurring after the participant has signed the ICF through the last safety visit or at least 30 days after the last application of study cream must be reported to the sponsor (or designee) immediately without undue delay but not later than **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately without undue delay but not later than 24 hours of obtaining knowledge of the update.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or more than 30 days after the last application of study cream. However, if the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study cream or study participation, then the investigator must notify the sponsor (or designee) immediately but no later than 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 (as defined in Section 9.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

If the SAE is not documented in the RSI of the IB for the study cream (new occurrence) and is thought to be related to the study cream, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same study cream that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities including EudraVigilance, as applicable, and relevant ethics committees following the sponsor's (or

approved designee) SOPs in accordance with EU CTR No. 536/2014 and FDA 21 CFR Part 312 or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study cream under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety report notifications must be prepared by the sponsor for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF. • The investigator must report immediately but no later than 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for notifying Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor without undue delay but not later than 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. Once the EDC system is functional, the SAE report should be retroactively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form or Study Reference Manual for details and for the email address or fax number). • Incyte Pharmacovigilance will issue queries for missing or discrepant information directly into the applicable EDC system (primary method), or via a Data Clarification Form. • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study cream because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs. • Contact information for SAE reporting can be found in the Study Reference Manual.

9.5. Potential Drug-Induced Liver Injury

Not applicable.

9.6. Events of Clinical Interest

Not applicable.

9.6.1. Adverse Events of Special Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

In a medical emergency during the study, if the investigator deems it necessary to determine optimal medical management of the participant, emergency unblinding will be performed exclusively by the principal investigator and subinvestigator as described in the IRT Manual.

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

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

9.8. Pregnancy

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

- The study cream must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee immediately but no later than **24 hours** of learning of the pregnancy.

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

Any SAE occurring during the pregnancy of a study participant must be recorded and reported as described in Section 9.4.

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

9.9. Warnings and Precautions

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

9.10. Product Complaints

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

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

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

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

9.11. Treatment of Overdose

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

10. STATISTICS

10.1. Sample Size Determination

Approximately 225 participants will be enrolled in this study and randomized 2:1 to ruxolitinib 1.5% cream or vehicle cream and stratified by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW or Europe).

The sample size was calculated to provide sufficient power to detect a difference between the treatment groups in the coprimary and key secondary endpoints. The assumptions and powers for different endpoints are provided in Table 9. The assumed response rates are derived from the overall and subgroup analyses (population: baseline scores of Itch NRS ≥ 4, EASI > 7, post-TCS and -TCI, and IGA = 3) in 2 Phase 3 AD studies, INCB 18424-303 and INCB 18424-304. Fisher exact test was used to provide a conservative evaluation of statistical power. Using a 2-sided α of 0.05, the sample size will have > 95% power to detect a difference in the coprimary endpoints, EASI75 and IGA-TS response rates between the treatment groups, and > 95% power for all key secondary endpoints.

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

Table 9: Powering for Coprimary and Key Secondary Endpoints

Variable	Response Rates in Ruxolitinib 1.5% BID	Response Rates in Vehicle	Power: Ruxolitinib vs Vehicle
EASI75	70%	15%	> 95%
IGA-TS	60%	10%	> 95%
ITCH4 at Week 8	50%	15%	> 95%
ITCH4 on Day 7	40%	12%	> 95%
ITCH4 on Day 3	35%	10%	> 95%
ITCH4 on Day 2	20%	3%	> 95%

10.2. Populations for Analysis

The populations for analysis are provided in Table 10.

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 assigned at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol. In general, the following are important Protocol deviations that may significantly affect the primary analysis: • Missing data for any of the coprimary endpoints. • Overall application compliance less than 80% during the VC period. Participants with 1 or more such deviations will be excluded from the PP population. In addition, important Protocol deviations related to inclusion/exclusion criteria, discontinuation criteria, and use of prohibited concomitant medications will be reviewed. Decisions as to whether any of these deviations warrant exclusion from the PP population will be made prior to unblinding.
VCE primary	The VCE primary population includes all participants who entered the VCE period and applied study cream at least once during the VCE period. Participants will be analyzed according to the treatment assigned at randomization. For participants who enter the escape arm, only information prior to entry to the escape arm will be presented.
VCE escape	The VCE escape population includes all participants in the VCE primary population who moved to the ruxolitinib 1.5% cream BID open-label escape arm.
Safety	The safety population includes all participants who applied study cream at least once. Treatment groups for this population will be determined according to the actual treatment the participant applied on Day 1.
PK-evaluable	The PK-evaluable population includes participants who applied ruxolitinib 1.5% cream at least once and provided at least 1 postbaseline blood sample for PK analysis. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

10.3. Level of Significance

For the coprimary and key secondary endpoints, the overall 2-sided Type I error is 0.05.

The key secondary endpoints are tested in a fixed sequence as follows if the null hypotheses for both coprimary endpoints (EASI75 and IGA-TS) are rejected:

1. Proportion of participants with ITCH4 from baseline at Week 8
2. Proportion of participants with ITCH4 from baseline on Day 7
3. Proportion of participants with ITCH4 from baseline on Day 3
4. Proportion of participants with ITCH4 from baseline on Day 2

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary analysis will be based on the ITT population. The primary alternative hypothesis (superiority of ruxolitinib 1.5% cream BID compared with vehicle cream BID) will be tested using a CMH test stratified by baseline EASI score and geographic region. The p-values and overall odds ratio with 95% CI between the ruxolitinib 1.5% cream BID and vehicle cream BID treatment groups will be provided. The p-values will be compared with the 2-sided α level of 0.05. A summary of EASI75 and IGA-TS rates will be reported for each treatment group. Stratum-adjusted rate differences (ruxolitinib 1.5% cream BID vs vehicle cream BID) on EASI75 and IGA-TS and the 95% CI will be computed using Mantel-Haenszel weights (Mantel and Haenszel 1959).

Participants with missing Week 8 scores for any reason will be defined as nonresponders for the primary analysis. Similar analyses will also be performed in the PP population for the coprimary endpoints. A longitudinal logistic regression with repeated measurements will be performed as a sensitivity analysis. In addition, other missing data imputation methods including multiple imputation and tipping point analysis may be conducted to examine the potential effects of missing data. Subgroup analysis by baseline characteristic (eg, geographic region, age, gender, race, baseline EASI score, season the participant was enrolled, prior cyclosporine therapy, and intertriginous involvement at baseline) will be performed. Details will be provided in the SAP.

10.4.1.1. Primary Estimand

The proportion of participants within each treatment group who achieve the coprimary endpoints, assuming participants with missing Week 8 assessments due to any reasons are nonresponders, will be the primary estimand. The 5 attributes and the strategies associated with the defined intercurrent events are detailed in Table 11.

Table 11: Primary Estimand

Estimand Attribute	**Definition**		
Treatment effect	Ruxolitinib 1.5% cream BID vs vehicle cream BID		
Population	Participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs (as defined by study inclusion/exclusion criteria)		
Variable	Apply to the coprimary endpoints		
Intercurrent events	**Events**	**Strategy**	**Rationale (if needed)**
	Treatment discontinuation due to any reason	Composite strategy	Participants who discontinue treatment due to any reason prior to Week 8 will be considered as treatment failures (ie, nonresponders) after the intercurrent event. Therefore, composite strategy is used for this type of intercurrent event.
Population-level summary	Stratum-adjusted response proportions difference between–treatment groups		

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 following the order as specified in Section 10.3.

The baseline Itch NRS score for by-visit summaries will be determined by averaging the 7 daily NRS scores directly before Day 1 (Day –7 to Day –1). The by-visit Itch NRS score for postbaseline visits will be determined by averaging the 7 daily NRS scores directly before the visit day. If 4 or more daily scores are missing (out of the 7), the Itch NRS score at the visit will be set to missing. The key secondary endpoint of Itch NRS score responses at Week 8 will be analyzed the same way as the primary estimand.

For all daily itch-related analyses, including time to achieve Itch NRS score improvement of at least 2 or 4 points, baseline will be defined as the last available Itch NRS score during the week prior to Day 1 (Day −7 to Day −1). For the key secondary endpoints of Itch NRS score responses on Day 7, Day 3, and Day 2, all participants who are missing Day 7, Day 3, and/or Day 2 daily Itch NRS scores will be imputed using multiple imputation by fully conditional specification method. The variables to be included in the imputation regression model are treatment group, stratification factors, baseline itch score, and postbaseline daily itch score on Day 1 to Day 7. The details of the multiple imputation, including number of imputations and seed number, will be specified in the SAP. After the missing values have been imputed, the binary variable for the ≥ 4-point improvement in Itch NRS score on Day 7, Day 3, and Day 2 will be derived. The CMH

method specified in Section 10.4.1 will be applied to each imputed dataset, and then the results will be combined for the inference.

Table 12 summarizes the analytical strategies that will be conducted in the key secondary endpoints.

Table 12: Analytical Strategies for the Key Secondary Endpoints

Key Secondary Endpoints	Analysis Strategy for Missing Data	Missing Data Imputation Method
ITCH4 at Week 8	Composite: Set to nonresponder	Nonresponder imputation
ITCH4 on Day 7, Day 3, and Day 2	Hypothetical: Set to missing	Multiple imputation

For the time to achieve ITCH2 and ITCH4 from baseline, a log-rank test stratified by baseline EASI score and geographic region will be used for between–treatment group comparisons. The hazard ratio and its 95% CI will be estimated based on the stratified Cox regression model using Efron's method accounting for ties. Kaplan-Meier curves will be presented by treatment group. The number of participants, number of events, and number of censorings will be summarized by treatment group. The Kaplan-Meier estimate of median time will be presented with its 95% CI. The 95% CI will be calculated using the method by Brookmeyer and Crowley (1982).

All other secondary efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. The CMH test specified in the coprimary 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.

The endpoints for participants who entered the escape arm will be summarized in the VCE escape population, different from the analyses in the VCE primary population.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population.

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first application of study cream and no later than 30 days after the Week 24 or ET visit. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study cream administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v5.0 using Grades 1 through 5.

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

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time.

10.5. Interim Analysis

No formal interim analysis is planned for this study.

10.6. Analysis Plan

The following analyses will be performed:

- The primary analysis will occur after the primary database lock, when all participants have completed the VC period (ie, up to Week 8). The sponsor will be unblinded after the primary database lock; however, investigators and participants will remain blinded to the individual study treatment assignment.
- The final analysis will occur when all participants have completed or withdrawn from the study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator. All documents must be reviewed and approved by the IRB/IEC and health authorities before the study is initiated. In accordance with EU CTR No. 536/2014, the sponsor will be responsible for submitting all documents in participating countries.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Recording and documenting AEs or laboratory abnormalities identified in the Protocol as critical to the safety evaluation and reporting them to the sponsor according to the reporting requirements specified in the Protocol.
  - Recording and documenting all AEs, unless the Protocol provides different guidance in Section 9.
  - Reporting to the sponsor all SAEs occurring to participants treated by them in the clinical study unless the Protocol provides different guidance in Section 9.
  - Reporting an SAE to the sponsor per Section 9 procedures and timelines if they become aware of an SAE with a suspected causal relationship to the study cream that occurs after the end of the study.
  - 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.
  - Ensuring (along with the sponsor) that the clinical study is conducted in accordance with the Protocol and with the principles of GCP.
  - 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.
  - Ensuring study-site compliance with the requirements of EU CTR No. 536/2014.
  - Assigning tasks among the members of the team of investigators in a way that does not compromise the safety of participants or the reliability and robustness of the data generated at the clinical study site.

- The investigator will adhere 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.
  - The investigator will retain the content of the clinical trial master file, essential documents, AE documentation, and medical and other study records in accordance with all local, national, and regulatory laws but for a minimum period of at least 30 years after completion or discontinuation of the study or as described in the final executed copy of the individual site agreement, or 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 formal discontinuation of clinical development of the test article and the regulatory authority is notified, whichever is longer, to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

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

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

The investigator will be responsible for the following:

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

  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.

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

11.3. Data Quality Assurance

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

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

11.4. Data Privacy and Confidentiality of Study Records

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

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

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

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

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

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

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

11.7. Study and Site Closure

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

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

Further, reasons for the early closure of a study site (eg, premature termination) by the sponsor, investigator, or the IRB/IEC may include but are not limited to the following:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or site agreement, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.
- Circumstances beyond the control of the sponsor or investigator that make it unreasonable to require the continuation of the study or site.
- Failure to carry out the study in the interest of the health of the participants.
- Failure to demonstrate that the continuation of an IRB-/IEC-approved study (ie, the IRB/IEC had previously issued a positive decision on the study) has scientific merit.
- Financial reasons (eg, the sponsor is declared insolvent or a bankruptcy petition has been filed).

12. REFERENCES

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

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

For male participants of reproductive potential[b]

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

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

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

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

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

For female participants who are WOCBP

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

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

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

Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. REQUIRED LABORATORY ANALYTES

<table>
<tr><th>Chemistry</th><th>Hematology</th><th>Serology</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)</td><td>Complete blood count, including:
• Hemoglobin
• Hematocrit
• Mean corpuscular volume
• Mean platelet volume
• Platelet count
• Red blood cell count
• White blood cell count</td><td>HIV antibody</td></tr>
<tr><td rowspan="2">Differential count (absolute and %), including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td><td>Pregnancy Testing</td></tr>
<tr><td>Human chorionic gonadotropin (WOCBP)
FSH (women of nonchildbearing potential only)</td></tr>
</table>

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	30 NOV 2023
Amendment 2	08 AUG 2024

Amendment 2 (08 AUG 2024)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to incorporate changes requested by regulatory agencies and ethics committees from the EU (Amendment 1-EU dated 20 JUN 2024) and Switzerland (Amendment 1-CH dated 21 JUN 2024). Additional changes are summarized below.

1. **Section 2.1.1, Ruxolitinib Cream**

   Description of change: Clarified reference to the IB for details on the nonclinical and clinical development.

   Rationale for change: Health Authority request.

2. **Section 2.2.1, Scientific Rationale for Study Design**

   Description of change: Added justification for the 20% BSA upper limit.

   Rationale for change: Health Authority request.

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

   Description of change: Added text to elaborate on the statement that ruxolitinib cream was well tolerated in the 2 Phase 3 AD studies in adolescents and adults.

   Rationale for change: Health Authority request.

4. **Section 5.1, Inclusion Criteria**

   Description of change: Added text to Inclusion Criterion 11 to clarify that female study participants must not be lactating or breastfeeding to be enrolled on study.

   Rationale for change: Health Authority request.

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

   Description of change: Added further details on the conditions for carrying out the double-blind procedures and use of vehicle cream as a control.

   Rationale for change: Health Authority request.

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

   Description of change: Modified the criteria of the application instructions to be reinforced by the investigator or a qualified designee, related to the estimated maximum daily dose used by participants.

   Rationale for change: Subsequent to Health Authority request for clarification of the maximum daily dose, the guidelines for usage were revised to align with those stated in the protocols of the pivotal AD studies INCB 18424-303 and INCB 18424-304 as well as to be consistent with the ruxolitinib cream Investigational Medicinal Product Dossier (Section 2.1.S.4.5).

7. **Section 8.3.4.2, Serology**

   Description of change: Added further details to provide information on management of participants who test positive for HIV.

   Rationale for change: Ethics Committee request.

8. **Section 9.2, Definition of Serious Adverse Event**

   Description of change: Modified wording to clarify definition of inpatient hospitalization and added evaluation relating to emergency department visits.

   Rational for change: To further clarify the definition of serious adverse event.

9. **Section 10.2, Populations for Analysis (Table 10: Populations for Analysis)**

   Description of change: Added details on the definition of the per-protocol population.

   Rationale for change: Health Authority request.

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

Amendment 1 (30 NOV 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to revise the language prohibiting the use of strong CYP3A4 inhibitors, to address FDA feedback on other ruxolitinib cream protocols, and to add an exploratory endpoint to assess the activity of ruxolitinib cream in intertriginous regions affected by AD. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 6.1, Study Treatments Administered (Table 6: Study Treatment Information)**

   Description of change: Removed of repetitive text regarding minimal threshold of at least 80% study cream application compliance, as well as specific timepoint of application time (ie, removed 10 AM). (This was previously described in the original Protocol.) Added footnote to Table 6 with regard to the EU's approval to use ruxolitinib for AD.

   Rationale for change: Protocol text simplification, in addition to providing updates per current regulatory environment.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period); Section 8.2.6.1, Itch Numeric Rating Scale; Section 8.2.6.1.1, Current Itch Numeric Rating Scale; Section 8.2.6.2, Skin Pain Numeric Rating Scale**

   Description of change: Removed current Itch NRS 12 hour timepoint assessment on Day 1. Added a required safety follow-up for Itch NRS and Skin Pain NRS.

   Rationale for change: Operational simplification in timing of Day 1 visit.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period, Table 4: Schedule of Activities: Vehicle-Controlled Extension Period/Escape Arm); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 8.2.2.1, Characterization of Atopic Dermatitis Involvement in Intertriginous Regions**

   Description of change: Added an exploratory endpoint to characterize the efficacy of ruxolitinib cream in participants with moderate AD and intertriginous region involvement.

   Rationale for change: To allow further characterization of ruxolitinib cream activity.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period); Section 8.1.4, eDiary and Reminder Cards; Section 8.2.6, Patient-Reported Outcome Assessments**

   Description of change: The utility of bring your own device option for the PRO at home assessments has been removed from the Protocol.

   Rationale for change: Operational decision to switch to Electronic Clinical Outcome Assessment vendor services.

5. **Section 5.2, Exclusion Criteria 5 and 10; Section 6.6.4, Prohibited Medications and Procedures**

   Description of change: Incorporated Exclusion Criterion #10 into Exclusion Criterion #5, and modified the washout period regarding strong cytochrome P450 3A4 inhibitors. Added the use of strong systemic CYP3A4 inhibitors to the list of prohibited medications.

   Rationale for change: To align with feedback from FDA on other recent ruxolitinib cream Protocol updates.

6. **Section 8.5.1, Serum for Biomarker Assessments**

   Description of change: Added text elaborating that serum samples on Day 1 must be collected prior to the first study cream application.

   Rationale of change: Clarification.

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

Signature Page for VV-CLIN-024736 v3.0

Approval Task	[redacted] Approver [redacted]of Inflammation and AutoImmunity Group 08-Aug-2024 19:24:27 GMT+0000

Approval Task	[redacted] Document Preparer [redacted] Clinical Research Scientist 08-Aug-2024 19:57:34 GMT+0000

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