Official Title: A Phase 3, Open-Label, One-Year Safety Study of Ruxolitinib Cream in Adolescents (Ages ≥ 12 Years to < 18 Years) With Atopic Dermatitis

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Clinical Study Protocol

INCB 18424-315

A Phase 3, Open-Label, One-Year Safety Study of Ruxolitinib Cream in Adolescents (Ages ≥ 12 Years to < 18 Years) With Atopic Dermatitis

Product:	**Ruxolitinib cream**
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Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**04 MAR 2022**
Amendment 1:	**30 NOV 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-315 Protocol Amendment 1 (dated 30 NOV 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	Clinical Study Report
CT	continuous treatment
CTCAE	Common Terminology Criteria for Adverse Events
DVT	deep vein thrombosis
EASI	Eczema Area and Severity Index
EASI75	≥75% improvement in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act of 1996
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 Numerical Rating Scale
JAK	Janus kinase
LTS	long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
PD	pharmacodynamic(s)
PDE4	phosphodiesterase 4
PE	pulmonary embolism
PK	pharmacokinetic(s)
RSI	Reference Safety Information
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
STD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	ultraviolet
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title: A Phase 3, Open-Label, One-Year Safety Study of Ruxolitinib Cream in Adolescents (Ages ≥ 12 Years to < 18 Years) With Atopic Dermatitis

Protocol Number: INCB 18424-315

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the long-term safety and tolerability of ruxolitinib cream in adolescents with AD.	Incidence of TEAEs, assessed by monitoring the type, frequency, and severity of AEs.
Secondary	
To further evaluate the long-term safety and tolerability of ruxolitinib cream in adolescents with AD.	Changes in vital signs, height, weight, and laboratory data for hematology and serum chemistry.
To characterize the PK of ruxolitinib cream in adolescents with AD.	Trough concentrations of ruxolitinib at each postbaseline visit.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Topical short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromised patients 12 to 17 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
Population	Male and female participants 12 to 17 years of age with a diagnosis of AD for at least 2 years, a total IGA score of 2 or 3, and BSA involvement of 3% to 20% (excluding the scalp).
Number of Participants	Approximately 100 participants will be enrolled.
Study Design	Open-label, single-group, LTS study.
Estimated Duration of Study Participation	Participants will take part in the study for up to approximately 60 weeks: 28 days in the screening period, 8 weeks in the CT period, 44 weeks in the LTS period, and 30 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:

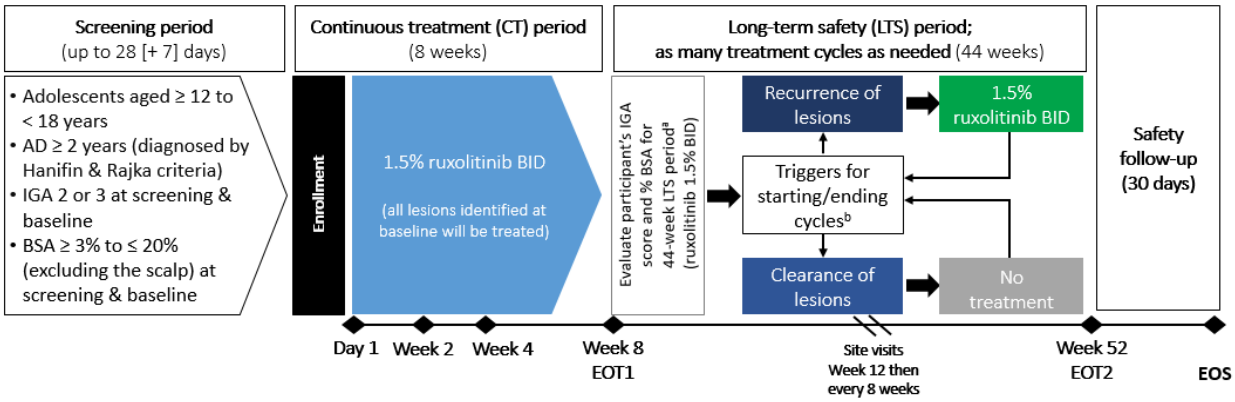
This is a Phase 3, open-label, 1-year safety study of ruxolitinib cream in approximately 100 adolescents (ages ≥ 12 years to < 18 years) with AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (see study design schema in Figure 1).

All participants will apply ruxolitinib cream at the FDA-approved strength (1.5%) BID, starting with an 8-week CT period during which participants will treat all baseline AD lesions BID, regardless of whether or not the lesion(s) improve, followed by a 44-week LTS period during which participants will only treat active AD lesions.

All participants will have a safety follow-up visit 30 to 37 days following the end of treatment (Week 52/EOT2 or ET) to evaluate safety and duration of response except for participants who have been in an observation/no treatment cycle with a total IGA score of 0 from Week 48 or earlier until Week 52, for whom the Week 52/EOT2 visit will also count as the safety follow-up visit.

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

Figure 1: Study Design Schema



[a] At Week 8, to qualify for the LTS period, an IGA score of 0 to 4 and %BSA affected by AD of 0% to ≤ 20% will be required.
[b] Treatment is ceased 3 days after clearing of AD lesions. Treatment is restarted if AD lesions recur. There is no limit to the number of treatment cycles during the 44-week LTS period.

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

Table 3: Schedule of Activities: Continuous Treatment Period

Visit Day (Range)	Screening	CT				Notes
	Days −28 to -1	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8/EOT1[a] or ET (± 3 d)	
Administrative procedures						
Informed consent (including assent)	X					Section 8.1.1
Contact IRT	X	X	X	X	X	Section 8.1.3
Inclusion/exclusion criteria review	X	X				Section 5
Demography and general medical history	X					Section 8.1.5.1
Relevant AD medical and treatment history	X					Section 8.1.5.2
Prior/concomitant medications and procedures	X*	X	X	X	X	Section 6.6 *For prior medications that require a 4-week washout period (Section 5.2, Exclusion Criterion 5b), a 35-day screening period is allowed.
Apply study cream at site		X	X	X	X*	Section 6.1.1; at the Day 1 visit, the participant should apply the first (morning) application at the site under direct site staff supervision. At all other visits, the participant may apply either of the 2 daily doses at the site, as long as it is at least 4 hours since the previous dose was applied (see Section 8.4). *Not applicable to the Week 8 visit if IGA score = 0 or to the ET visit.
Weigh/dispense study cream and distribute reminder		X	X	X	X*	Section 6.1.1 and Section 8.1.4 *Not applicable to the ET visit.
Collect/weigh returned study cream and review study cream eDiary compliance			X	X	X	Section 6.1.1 and Section 8.1.4
Assess study cream application compliance			X	X	X	Section 6.4
Assess Itch NRS eDiary compliance	eDiary compliance should be assessed routinely					Section 8.2.4

Table 3: Schedule of Activities: Continuous Treatment Period (Continued)

Visit Day (Range)	Screening	CT				Notes
	Days −28 to -1	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8/EOT1[a] or ET (± 3 d)	
Safety assessments						
AE assessments and targeted physical examination	X	X	X	X	X*	Section 8.3.1 and Section 8.3.2.2; body systems with symptoms should be physically examined. *Targeted physical examination not performed at ET visit.
Comprehensive physical examination	X				X*	Section 8.3.2.1 *For the ET visit only.
Body height and weight		X			X	Section 8.3.3; height should be measured with a stadiometer and recorded.
Vital signs	X	X	X	X	X	Section 8.3.3; vital signs should be taken before blood sampling and other procedures.
12-lead ECG	X					Section 8.3.4; 12-lead ECG performed within 2 months before baseline is acceptable.
Efficacy assessments						
%BSA affected by AD	X	X	X	X	X*	Section 8.2.2 *At Week 8, to qualify for the LTS period, the %BSA range must be 0% to ≤ 20%.
Total IGA and facial IGA	X	X	X	X	X*	Section 8.2.3 *At Week 8, there are no restrictions on IGA score to qualify for the LTS period.
EASI	X	X	X	X	X	Section 8.2.5
Itch NRS	eDiary is completed each evening from screening through the last application of study cream during the CT period (night before Week 8 visit).					Section 8.2.4

Table 3: Schedule of Activities: Continuous Treatment Period (Continued)

Visit Day (Range)	Screening	CT				Notes
	Days −28 to -1	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8/EOT1[a] or ET (± 3 d)	
Laboratory assessments						
Serum chemistries	X	X*	X	X	X	Section 8.3.5 *Perform Day 1 testing only if the interval between Day 1 and the date of the screening laboratory test is > 2 weeks.
Hematology	X	X*	X	X	X	Section 8.3.5 *Perform Day 1 testing only if the interval between Day 1 and the date of the screening laboratory test is > 2 weeks.
Serology	X					Section 8.3.5.2; HIV antibody.
Pregnancy testing	X*	X		X	X	Section 8.3.5.1 *WOCBP will have a serum pregnancy test at screening and a urine test at all other visits. A positive urine test must be confirmed with a serum test.
PK blood and saliva sampling (trough)			Blood and saliva	Blood and saliva	Saliva only	Section 8.4; collected prior to study cream application at the clinic; the time of prior study cream application is to be recorded in the eCRF. Blood samples must not be drawn from an area that has been treated with study cream (or participants must not apply study cream from the previous application of study cream on the immediate body area where blood is to be drawn).

[a] All assessments for the Week 8/EOT1 visit must be performed before participants may enter the LTS period.

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

Visit Day (Range)	LTS			Safety Follow-Up	Notes
	Weeks 12, 20, 28, 36, and 44 (± 7 d)	Week 52/EOT2 or ET (± 7 d)	Unscheduled Visits	30-37 d After Week 52/EOT2 or ET Visit[a]	
Administrative procedures					
Contact IRT	X	X	X	X	Section 8.1.3
Prior/concomitant medications and procedures	X	X	X	X	Section 6.6
Apply study cream at site	X				Section 6.1.1; only for participants with active AD lesions at time of visit.
Weigh/dispense study cream and distribute reminder	X				Section 6.1.1 and Section 8.1.4
Collect/weigh returned study cream and review study cream eDiary compliance	X	X			Section 6.1.1 and Section 6.4
Record start and end dates of treatment cycle(s)	X	X			Section 6.1; the start/end date will have been recorded by the participant. The end date should be 3 days after lesions clear; however, if this 3-day window is during a study visit and total IGA score = 0, stop treatment and record the date of the study visit as the treatment cycle end date.
Assess study cream application compliance	X	X			Section 6.4
Assess Itch NRS eDiary compliance	eDiary compliance should be assessed routinely				Section 8.2.4
Safety assessments					
AE assessments and targeted physical examination	X	X*	X	X	Section 8.3.1 and Section 8.3.2.2; body systems with symptoms should be physically examined. *Targeted physical examination not performed at the Week 52/EOT2 or ET visit.
Comprehensive physical examination		X			Section 8.3.2.1
Body height and weight	X*	X			Section 8.3.3; height should be measured with a stadiometer and recorded *Week 28 only.
Vital signs	X	X	X	X	Section 8.3.3; vital signs should be taken before blood/saliva sampling and other procedures.

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

Visit Day (Range)	LTS			Safety Follow-Up	Notes
	Weeks 12, 20, 28, 36, and 44 (± 7 d)	Week 52/EOT2 or ET (± 7 d)	Unscheduled Visits	30-37 d After Week 52/EOT2 or ET Visit[a]	
Disease severity assessments					
%BSA affected by AD	X	X	X	X	Section 8.2.2
Total IGA and facial IGA	X	X	X	X	Section 8.2.3
EASI	X	X	X	X	Section 8.2.5
Itch NRS	eDiary is completed each evening through the last application of study cream during the LTS period.				Section 8.2.4
Laboratory assessments					
Serum chemistries	X	X	X	X	Section 8.3.5
Hematology	X	X	X	X	Section 8.3.5
Pregnancy testing	X	X	X	X	Section 8.3.5.1; WOCBP will have a urine test at all visits. A positive urine test must be confirmed by a serum test.
PK saliva sampling (trough)	X*/†	X†/‡			Section 8.4 *Collected prior to study cream application at the clinic. †The time of prior study cream application is to be recorded in the eCRF. ‡Not to be collected at the ET visit.

[a] Except for participants who have been in an observation/no treatment cycle with a total IGA score of 0 (clear) from Week 48 or earlier until Week 52; such participants should complete the Week 52/EOT2 visit and this will also count as the safety follow-up visit.

2. INTRODUCTION

2.1. Background

Atopic dermatitis is a chronic, recurring, inflammatory, and highly pruritic skin condition that affects up to 25% of children and up to 12% of adults worldwide (Eichenfield et al 2014, Hanifin et al 2007, Harrop et al 2007, Rönmark et al 2012, Vinding et al 2014) and is one of the most common dermatoses encountered by pediatric health care providers. Although not life-threatening, patients with AD are at 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 and that are also both effective and safe. Moderate to potent topical corticosteroids and calcineurin inhibitors have well-known safety restrictions limiting their use to 4 and 8 weeks, respectively. In addition, a PDE4 inhibitor, 2% crisaborole (Eucrisa®) ointment, is approved in the US for patients aged 3 months and older with mild to moderate AD and has no such safety limitations but was shown to have modest efficacy (Eucrisa 2020).

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 US. 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.

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate that was recently approved in the US for the topical short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (Opzelura™ 2022). This approval was based on data from 2 Phase 3 studies in adolescents and adults with AD (INCB 18424-303 and -304; Papp et al 2021) 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.

2.2. Study Rationale

The primary purpose of this study is to collect additional long-term safety data regarding the types and frequencies of TEAEs occurring in adolescents with AD who are treated with ruxolitinib 1.5% cream BID. In the Phase 3 studies, 114 adolescents were treated with ruxolitinib 1.5% cream BID, and the safety profile was similar to that in adults. This is a Post-Marketing Requirement study for the FDA.

2.2.1. Scientific Rationale for Study Design

As the intent of this study is to further assess the safety of ruxolitinib 1.5% cream BID in adolescents with AD in addition to what was studied in the Phase 3 studies, INCB 18424-303 and INCB 18424-304, the study population has been based on that in the Phase 3 studies, namely adolescents aged ≥ 12 to < 18 years of age with AD for at least 2 years and affecting 3% to 20% BSA (excluding the scalp) plus a total IGA score of 2 or 3.

In addition, given the recent concerns about the potential thromboembolic and cancer risks of oral JAK inhibitors that are currently approved as treatments for rheumatoid arthritis (Olumiant 2021, Xeljanz 2021), the exclusion criteria have been augmented where necessary to exclude anyone with current or a history of venous thromboembolism (DVT or PE), major adverse cardiovascular events, or malignancies.

The primary and secondary objectives and endpoints focus on further assessing the safety and tolerability of ruxolitinib 1.5% cream BID in adolescents through assessment of TEAEs, vital signs (in particular height and weight), laboratory data for hematology and serum chemistry, and PK (trough concentrations of ruxolitinib).

2.2.2. Justification for Treatment Regimen

All participants will apply ruxolitinib cream at the FDA-approved strength (1.5%) and application frequency (BID) using the same treatment paradigm as the Phase 3 AD studies, namely starting with an 8-week CT period during which participants will treat all baseline AD lesions, regardless of whether or not the lesion(s) improve, followed by a 44-week LTS period during which participants will only treat active AD lesions. Modifications to the treatment regimen will not be allowed, as in the Phase 3 AD studies (refer to Section 6.5, Dose Modifications, for more details).

2.3. Benefit/Risk Assessment

In the Phase 3 AD studies, ruxolitinib 1.5% cream BID rapidly and effectively improved both the signs and symptoms of AD in adults and adolescents, being statistically significantly superior to vehicle cream BID at the end of the vehicle-controlled period (Week 8) for IGA-TS, EASI75, and ≥ 4-point improvement in Itch NRS score. The antipruritic effect of ruxolitinib 1.5% cream BID showed a rapid onset with evidence of a treatment effect on daily Itch NRS scores as early as Day 1 (ie, within 12 hours after the first application of study cream). The disease course (assessed by IGA scores and %BSA affected by AD at study visits during Weeks 8 through 52) was well-controlled throughout the entirety of the LTS period of the study. The treatment effects of ruxolitinib 1.5% cream BID on IGA-TS, EASI75, and Itch NRS score were consistently observed across both adult and adolescent subgroups.

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

Results from dermal safety studies in healthy adult participants (INCB 18424-104, -105, -106, -107, and -108) to evaluate local tolerability demonstrated that ruxolitinib 1.5% cream did not cause sensitization and was only slightly irritating under exaggerated testing conditions (occlusive application). In addition, ruxolitinib 1.5% cream was not phototoxic and did not induce photosensitization. This was further confirmed by the Phase 3 (INCB 18424-303 and -304) safety data where ruxolitinib 1.5% cream BID was well-tolerated at the application sites with infrequently reported application site reactions. The most frequently reported application site reaction events were application site pain (lowest level terms were primarily application site burning or application site stinging) and application site pruritus; each of these events occurred in a lower proportion of participants in the ruxolitinib 1.5% cream BID treatment group (application site pain, 0.7%; application site pruritus, 0.6%) compared with the vehicle cream treatment group (application site pain, 4.8%; application site pruritus, 2.8%) during the 8-week, vehicle-controlled period, which may be attributable to worsening of the underlying disease in the absence of active drug treatment.

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

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

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the long-term safety and tolerability of ruxolitinib cream in adolescents with AD.	Incidence of TEAEs, assessed by monitoring the type, frequency, and severity of AEs.
Secondary	
To further evaluate the long-term safety and tolerability of ruxolitinib cream in adolescents with AD.	Changes in vital signs, height, weight, and laboratory data for hematology and serum chemistry.
To characterize the PK of ruxolitinib cream in adolescents with AD.	Trough concentrations of ruxolitinib at each postbaseline visit.
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, open-label, 1-year safety study of ruxolitinib cream in adolescents (ages ≥ 12 years to < 18 years) with AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (see study design schema in Figure 1). The study will be conducted at approximately 40 sites in North America and Europe.

Approximately 100 participants with a diagnosis of AD (as defined by the Hanifin and Rajka [1980] criteria) with a duration of disease of at least 2 years, a total IGA score of 2 or 3, and %BSA affected by AD of 3% to 20% (excluding the scalp) will be enrolled.

All participants will apply ruxolitinib cream at the FDA-approved strength (1.5%) BID using the same treatment paradigm as the INCB 18424-303 and -304 Phase 3 AD studies, namely starting with an 8-week CT period during which participants will treat all baseline AD lesions, regardless of whether or not the lesion(s) improve, followed by a 44-week LTS period during which participants will only treat active AD lesions.

Participants who complete the Week 8 assessments with no safety concerns and with %BSA affected by AD no greater than 20% will continue into the LTS period.

During the LTS period (ie, starting at the Week 8 visit), the treatment regimen will continue to be ruxolitinib 1.5% cream BID; however, participants will only treat active AD lesions. Participants will have the next study visit at Week 12, and then subsequent study visits will occur every 8 weeks until the end of the study (44 weeks total in the LTS period and 52 weeks total in the study). At those study visits, AD lesions will be evaluated by the investigator to confirm if the participant still requires continuation of therapy (total IGA score ≥ 1) or can otherwise (re)enter the observation/no treatment cycle (total IGA score = 0). Refer to Section 6.1 for further details.

Participants will be assessed for the safety and tolerability of ruxolitinib cream throughout the study by monitoring the type, frequency, and severity of AEs; performing physical examinations; measuring vital signs, including height and weight; and conducting clinical laboratory assessments, as outlined in the SoA (see Table 3 [CT period] and Table 4 [LTS period]). In addition, the trough ruxolitinib concentration will be measured at various timepoints throughout the study (see Table 3 [CT period] and Table 4 [LTS period]), and its relationship with select hematology parameters such as platelet count, MPV, hemoglobin level, and neutrophil count will be assessed.

Several exploratory disease severity assessments will be conducted throughout the study (see Table 3 [CT period] and Table 4 [LTS period]) to evaluate the long-term efficacy of ruxolitinib cream, namely [redacted]

All participants will have a safety follow-up visit 30 to 37 days following the end of treatment (Week 52/EOT2 or ET) to evaluate safety and duration of response except for participants who have been in an observation/no treatment cycle with a total IGA score of 0 from Week 48 or earlier until Week 52, for whom the Week 52/EOT2 visit will also count as the safety follow-up visit. See Section 8.8.1 for further details.

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

4.2. Overall Study Duration

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

Participants will participate in the study for a duration of up to approximately 60 weeks: 28 days in the screening period, 8 weeks in the CT period, 44 weeks in the LTS period, and 30 days in the safety follow-up period (see Figure 1).

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

4.3. Study Termination

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

The sponsor may terminate the study electively or if required by 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 the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

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

1. Adolescents aged ≥ 12 years to < 18 years (at the screening visit).
2. A diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria.
3. Duration of AD of at least 2 years.
4. Total IGA score of 2 to 3 at the screening and baseline visits.
5. Percent BSA (excluding the scalp) with AD involvement of 3% to 20% at the screening and baseline visits.
6. Atopic dermatitis not adequately controlled with other topical prescription therapies or when those therapies are not advisable. See Section 8.1.5.2 for further details.
7. Agree to discontinue all agents used to treat AD from screening through the final follow-up visit.
8. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of ruxolitinib cream and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first application of ruxolitinib 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 ruxolitinib cream and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. A female participant not considered to be of childbearing potential as defined in Appendix A is eligible.
9. Ability to comprehend and willingness to sign an ICF or written informed consent of the parent(s) or legal guardian(s) and written assent from the participant when possible.

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

5.2. Exclusion Criteria

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

1. An unstable course of AD (spontaneously improving or rapidly deteriorating) as determined by the investigator in the 4 weeks prior to baseline.
2. Concurrent conditions and history of other diseases:
    a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
    b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
    c. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox) within 1 week before baseline.
    d. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton syndrome), pigmentation, or extensive scarring that, in the opinion of the investigator, may interfere with the evaluation of AD lesions or compromise participant safety.
    e. Presence of AD lesions only on the hands or feet without prior history of involvement of other classic areas of involvement such as the face or the flexural folds.
    f. Other types of eczema.
    g. Current or history of hepatitis B or C virus infection.
3. Any current and/or history of serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including application of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
    a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction or stroke within 6 months from Day 1 of study cream application, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mm Hg) unless approved by the medical monitor/sponsor.
    b. Current and/or history of malignancy in the 5 years preceding the baseline visit, except for adequately treated, nonmetastatic nonmelanoma skin cancer.
    c. Current and/or history of arterial or venous thrombosis, including DVT and PE.
    d. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.
4. Any of the following clinical laboratory test results at screening:
    a. Hemoglobin < 100 g/L (< 10 g/dL)
    b. Liver function tests:
        − AST or ALT ≥ 2.5 × ULN
        − Total bilirubin > 1.5 × ULN with the exception of Gilbert disease.
    c. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (using the CKD 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 baseline:
    a. 5 half-lives or 12 weeks, whichever is longer – biologic agents (eg, dupilumab). For biologic agents with washout periods longer than 12 weeks (eg, rituximab), consult the medical monitor.
    b. 4 weeks – systemic corticosteroids or adrenocorticotropic hormone analogues, cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
    c. 2 weeks – immunizations with live-attenuated vaccines; sedating antihistamines, unless on long-term stable regimen (nonsedating antihistamines are permitted).
    Note: Live-attenuated vaccines are not recommended during the CT period.
    Note: COVID-19 vaccination is allowed.
    d. 1 week – use of other topical treatments for AD (other than bland emollients, eg, Aveeno® creams, ointments, sprays, soap substitutes), such as topical antipruritics (eg, doxepin cream), corticosteroids, calcineurin inhibitors, PDE4 inhibitors, coal tar (shampoo), 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. Previously received systemic or topical JAK inhibitors (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).
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, which is thought by the investigator to potentially impact the participant's AD.
8. Pregnant or lactating, or considering pregnancy during the period of their study participation.
9. 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.
10. 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.
11. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before baseline with a strong CYP3A4 inhibitor.
12. Removed during Protocol Amendment 1.
13. Known allergy or reaction to any component of the study cream formulation.
14. In the opinion of the investigator unable or unlikely to comply with the administration schedule and study evaluations.
15. Committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.
16. Employees of the sponsor or investigator or are otherwise dependents of them.

5.3. Lifestyle Considerations

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

If sunscreen, makeup, or other cosmetics have been applied to the areas to be treated, participants should wash the treatment areas with mild soap and water and pat dry before application of study cream. See Section 6.6.1 for additional guidance.

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

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

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must 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 participant number.

5.5. Replacement of Participants

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

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

Study Treatment Name:	Ruxolitinib
Dosage Formulation:	Cream
Unit Strength:	1.5%
Route of Administration:	Topical
Administration Instructions:	BID. A thin film is applied to areas affected by AD in the morning and in the evening at least 1 hour before bedtime.
Packaging and Labeling:	Ruxolitinib cream will be provided in 60-g tubes. Each tube will be labeled as required per country requirements.
Storage:	Ambient (15°C-30°C/59°F-86°F)
Status of Treatment in Participating Countries:	Approved in the US[a]; investigational in all other countries

[a] Opzelura (ruxolitinib) cream.

Ruxolitinib cream study drug will be supplied in 60-g tubes and applied topically as a thin film BID (optimally at equal intervals, eg, ideally 12 hours apart but with at least 8 hours between applications) to the affected areas in the morning and in the evening, with the evening application at least 1 hour before bedtime.

At the baseline visit, an estimate of the %BSA to be treated will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. All AD areas identified at the baseline visit should continue to be treated through the end of the CT 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, and if there are no safety concerns, 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 CT 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. Approval to treat these additional areas may occur via telephone, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit. This is a close reflection of the clinical practice of managing AD in the outpatient setting. During the CT period, participants whose additional new areas to be treated in addition to the areas identified at the baseline visit exceed 20% BSA should be discontinued from study cream and complete the ET assessments.

During the LTS period (ie, starting at the Week 8 visit), participants will have study visits at Week 12 and then every 8 weeks until the end of the study (44 weeks total), with the final possible application being the evening application on the day before the Week 52 visit. At each

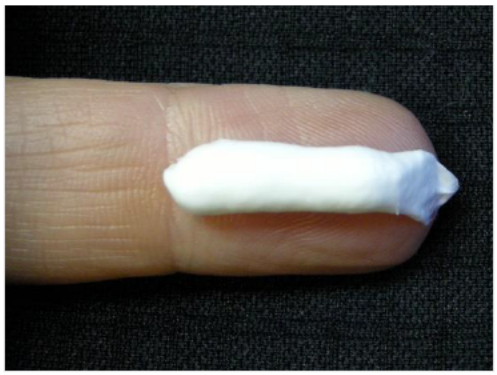
LTS period visit, AD lesions will be evaluated by the investigator to confirm whether the participant requires continuation of therapy (total IGA score ≥ 1) or can (re)enter the observation/no treatment cycle (total IGA score = 0). During the LTS period, only areas with active disease need to be treated. Participants who develop new or expanded areas of AD may treat these additional areas with approval by the investigator as long as the total treated BSA does not exceed 20% and there are no safety concerns regarding the additional application of study cream. Approval to treat additional areas may occur via telephone, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit.

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

6.1.1. Study Treatment Application Guidance

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

Figure 2: Study Cream Application Using a Fingertip



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

On the day of a visit, study cream will be applied in the clinic during the visit, under direct supervision of the site staff. The tube will be weighed before and after application to determine the participant's usage.

The Day 1 (baseline) visit should take place in the morning, so that the initial dose of study cream is applied in the clinic in the morning. For all other visits, the participant may apply either of the 2 daily doses at the site, as long as it is at least 4 hours since the previous dose was applied (see Section 8.4). Note that no study cream will be applied at any of the visits from Week 8 to Week 52 if the IGA is 0 (ie, no active AD lesions) or at the ET visit.

Application instructions will be provided by the site study staff, and the participants will record their daily applications via an eDiary. Participants must not apply study cream more often than

BID and should limit use to no more than one 60-g tube per week. Refer to the Study Manual for participant instructions for handling study cream.

6.2. Preparation, Handling, and Accountability

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

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

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

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

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

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study cream until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee 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 study cream 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 cream are included in the study materials provided to sites.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Treatment Compliance

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

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

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

6.5. Dose Modifications

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

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

6.5.1. Criteria and Procedures for Interruptions 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 cream.

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. Participants who experience a recurrence of the initial AEs upon restarting the study cream may need to permanently discontinue treatment with the study cream.

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

Instructions for interruption of study cream–related laboratory abnormalities are outlined in Table 7.

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

AE Related to Study Cream	Action Taken
Any Grade 3 laboratory abnormality	• 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. • Permanently discontinue study cream if laboratory abnormalities are confirmed. 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, compromised 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 related to the study cream (see Table 7).
- 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. 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 as follows:

- Non-AD medications and treatments that are taken between 35 days before the first application of study cream and 30 days after the last application of study cream.
- AD medications and treatments that are taken between 12 months before the start of Screening and 30 days after the last application of study cream.

Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered more than 30 days after the last application of study cream should be recorded for SAEs as defined in Section 9.2. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

The following are permitted during the study:

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

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

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

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Short-term use of systemic corticosteroids may be permitted to treat acute AEs (eg, asthma) during the LTS period, and the decision to keep the participant in the study (or to permanently discontinue study cream) will be made in consultation with the medical monitor.
- Participants may continue using sedating antihistaminic drugs as long as their use is part of a preexisting and well-established regimen. There are no restrictions for use of nonsedating antihistamines.
- Use of any over-the-counter, nonprescription preparations deemed acceptable by the investigator is permitted under an established and stable treatment regimen.
- Use of any prescription medication (including phytotherapeutic, herbal, or plant-derived preparations) is not permitted within 7 days before the baseline visit through the safety follow-up visit, unless deemed acceptable by the investigator.
- Immunizations with a live-attenuated vaccine are not recommended during the CT period (first 8 weeks) unless deemed necessary by the investigator.
- Allergen immunotherapy (desensitization) that is ongoing at a stable dose at the time of study entry may be continued while on study but only at the same dose.
- Bleach baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
- Participants should not take baths or showers within 2 hours after study cream application.
- Topical anti-infectives or other topical treatments applied to active AD lesions should not be used for at least 4 hours before and 2 hours after application of study cream.

6.6.3. Prohibited Medications and Procedures

The following are not permitted during the study:

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

6.7. Treatment After the End of the Study

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Lack of efficacy response during the LTS period (defined as no change/improvement in either %BSA or IGA score when treated continuously for any 8-week interval during the LTS period).
- Worsening of AD during either the CT period or the LTS period, to the point where the extent of AD to be treated (ie, all areas excluding the scalp) exceeds 20% BSA.
- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that 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:

- If, after 2 consecutive study visits and reinforcement of study cream application guidance by site staff, a participant's drug usage exceeds one 60-g tube per week, a participant who again fails to meet compliance benchmarks at a subsequent visit may be considered for withdrawal from the study. The medical monitor should be consulted for instruction on handling the participant.
- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study cream application in the investigator's opinion, the medical monitor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment prior to the Week 52/EOT2 study visit, the ET visit should be conducted. Reasonable efforts should be made to have the participant return for the safety follow-up visit. The date of the last application of study cream and the reason for discontinuation of study cream will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The ET visit should be performed and date recorded 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.

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

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

7.3. Lost to Follow-Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

See Appendix B for COVID-19 pandemic–related guidance.

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

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

8.1.2. Screening Procedures

Screening is the interval between signing the ICF/assent and the day the participant is enrolled in the study (Day 1). Informed consent (or assent) must be obtained before performing any study-specific procedures. Screening assessments for determination of eligibility may be performed over a period of up to 28 days, or up to 35 days for participants on prior medications requiring a 4-week washout period, as described in Section 5.2 (Exclusion Criterion 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 will be reviewed 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 enrollment will be used to determine eligibility. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, after recovery from an infection). The participant is not required to sign another ICF if the rescreening occurs within 35 days (screening period) of the previous ICF signature date.

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 site ID and participant number. Site staff should contact the IRT system to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study medication kit assignment. Additionally, the IRT system will be contacted at each regular study visit during both the CT period and the LTS period as indicated in Table 3 and Table 4, respectively, to update the study cream supply. The IRT system will also be used during the study visits to recalculate the amount of study cream to be dispensed if the participant's %BSA of AD lesions to be treated has increased (during the CT period) or has either increased or decreased (during the LTS period). Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminders and eDiaries

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

Qualified clinical study staff will review the participants' entries for compliance, as outlined in Section 6.4.

Participants will be provided with a reminder starting on Day 1 and at all CT and all LTS visits through Week 48. The reminder will indicate the date and time of the next visit and will also remind the participant that their morning application of study cream will be take place at the clinic under site supervision after blood or saliva collection for PK and safety evaluations have been completed.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. General medical history will include relevant medical or surgical treatment within the past 2 years that are considered to be clinically significant by the investigator. Treatment history for AD is covered in Section 8.1.5.2.

8.1.5.2. Disease Characteristics and Treatment History

An AD-targeted medical and treatment history will be collected at screening. Details regarding the participant's AD, including date of diagnosis and relevant disease characteristics, will be recorded. A medical history of other conditions related to AD will also be collected at this time.

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

Also, information about when the use of topical, prescription AD treatments within 12 months prior to screening was not advisable will be collected. An example of when other topical prescription therapies were not advisable is when the participant had previously experienced clinically relevant side effects/safety risks and/or skin tolerability issues that outweigh the potential treatment benefits and are the reason why a topical treatment cannot be initiated.

Acceptable documentation for the use of topical prescription treatments or when those treatments were not advisable (within 12 months prior to screening) include:

- Medical records, and/or
- Communication with the participant's treating physician, and/or
- Investigator documentation based on:
    - An interview with the participant or legal representative; and/or
    - Review of participant- or legal representative-reported medication history.

8.2. Efficacy Assessments

8.2.1. Health Economics

Not applicable.

8.2.2. Percent Body Surface Area Affected by Atopic Dermatitis

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

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

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

8.2.3. Investigator's Global Assessment

Investigator's Global Assessment is an overall eczema severity rating on a 0 to 4 scale that will be assessed for the whole body (total IGA) and for the face only (facial IGA) during site visits as outlined in the SoA (see Table 3 [CT period] and Table 4 [LTS period]). The area "Face" is defined as including the area on the forehead to the original hairline, on the cheek to the jawline vertically to the jawline and laterally from the corner of the mouth to the tragus. The area "Face" will not include the surface area of the lips, scalp, ears, or neck but will include the nose and eyelids. The severity strata 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 2012.

Participants must have a total IGA score of 2 or 3 at the screening and baseline visits to enroll in the study; there is no limitation for total or facial IGA score at Week 8 (baseline for the LTS period) to enter the LTS period.

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

[redacted]

8.2.4. Itch Numerical Rating Scale

The Itch NRS is a daily participant-reported measure (24-hour recall) of the worst level of itch intensity (Pruritus Resources). Participants will be asked to rate the itch severity of their AD by selecting a number from 0 (no itch) to 10 (worst imaginable itch) that best describes their worst level of itching in the past 24 hours as outlined in the SoA (see Table 3 [CT period] and Table 4 [LTS period]). Participants will be issued an eDiary in which to record itch severity. The participants will be instructed to complete the eDiary each night beginning on the day of screening through the last day of the LTS period. Detailed directions for the administration of an eDiary will be provided in the Study Manual.

8.2.5. Eczema Area and Severity Index

Atopic dermatitis will be assessed as outlined in the SoA (see Table 3 [CT period] and Table 4 [LTS period]) using the EASI scoring system (refer to the Study Manual), 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.

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 (Leshem et al 2015).

8.3. Safety Assessments

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

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last application of study drug. Adverse events for enrolled participants that

begin or worsen after informed consent/assent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study cream. Conditions that were already present at the time of informed consent/assent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

8.3.2. Physical Examinations

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. Physical examinations will be conducted at the timepoints listed in the SoA (see Table 3 [CT period] and Table 4 [LTS period]).

8.3.2.1. Comprehensive Physical Examination

At the screening visit and Week 52/EOT2 or ET visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

8.3.2.2. Targeted Physical Examination

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

8.3.3. Vital Signs, Height, and Weight

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

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

Height and weight will be assessed at the baseline, Week 8/EOT1/ET, Week 28, and Week 52/EOT2/ET visits. Height will be measured using a stadiometer. The stadiometer should be calibrated, and a wall-mounted one is recommended. Participants should be measured without socks and 3 measurements taken to the nearest 0.1 cm. The average of the 3 height measurements of individual participants should be recorded in the eCRF.

8.3.4. Electrocardiograms

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

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

8.3.5. Laboratory Assessments

See Table 9 for the list of clinical laboratory tests to be performed and the SoA (see Table 3 [CT period] and Table 4 [LTS period]) for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries and hematology assessments) and will store the samples for PK analysis. Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (see Table 3 [CT period] and Table 4 [LTS period]). Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

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

If screening laboratory assessments are performed less than or equal to 2 weeks before Day 1, then the Day 1 serum chemistry and hematology assessments do not need to be performed.

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

Table 9: Required Laboratory Analytes

Blood Chemistries	Hematology	Serology
Albumin Alkaline phosphatase ALT AST Blood urea nitrogen or urea Calcium Chloride Creatine kinase Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN)	Complete blood count, including: • Hemoglobin • Hematocrit • Mean corpuscular volume • MPV • Platelet count • Red blood cell count • White blood cell count Differential count (absolute and %), including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	HIV antibody **Pregnancy Testing** WOCBP will have a serum test at screening and a urine test at all other visits. A positive urine test must be confirmed by a serum test.

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

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. Urine pregnancy tests will be performed locally as outlined in the SoA (see Table 3 [CT period] and Table 4 [LTS period]), as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the 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 cream and continue participation in the study.

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

8.3.5.2. Serology

An HIV antibody assessment will be performed at the screening visit to rule out HIV infection. Generally, HIV tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.4. Pharmacokinetic Assessments

Pharmacokinetic blood and saliva samples will be collected from all participants at the visits and collection times shown in the SoA (see Table 3 [CT period] and Table 4 [LTS period]) and as noted in Table 10.

The exact date and time of the PK blood and saliva sampling and the date and time of the last application of study cream preceding the blood or saliva sample (if applicable) will be recorded in the eCRF.

Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Participants will receive reminders in advance of the study visit providing instructions to hold the application of study cream on the day of the visit and to record the time of the prior application of study cream.

Blood samples for PK must be drawn from an area that has not been treated with study cream, or if that is not possible, the participant must not apply study cream from the previous application of study cream on the immediate body area where blood is to be drawn (ie, for site visits in the morning, this means the application on the evening before [second dose of that day]; for site visits in the afternoon this means the application on the morning of the same day [first dose of that day]).

If blood is drawn from an area that has been treated with study cream, the site personnel must document the missed application at the location of the blood draw in the eCRF. After the PK blood or saliva sample is collected, participants will apply ruxolitinib 1.5% cream.

All analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

Table 10: Pharmacokinetic Blood and Saliva Sample Timing

Study Visit	Timing of Sample
CT period	Samples will be collected at any time prior to study cream application during study visits, but must be at least 4 hours after the previous application of study cream and after assessment of vital signs during the visit:
	• Blood and saliva samples
• Week 2	• Blood and saliva samples
• Week 4	• Saliva sample only
• Week 8/EOT1 or ET	
LTS period: Weeks 12, 20, 28, 36, 44, and 52/EOT2	Saliva samples will be collected at any time prior to study cream application during study visits, but must be at least 4 hours after the previous application of study cream and after assessment of vital signs during the visit. No blood samples will be collected during the LTS period.

8.5. Pharmacodynamic and Translational Assessments

Not applicable.

8.6. Unscheduled Visits

Unscheduled study visits may occur at any time medically warranted, including when participants develop new areas of AD (see Section 6.1). Any assessments performed at those visits should be recorded in the eCRF.

8.7. End of Treatment and/or Early Termination

The end of treatment for the CT period (EOT1) coincides with the Week 8 visit. At that time, if the participant continues into the LTS period, then the Week 8/EOT1 visit should be conducted. However, if the participant does not continue into the LTS period, the ET evaluations should be conducted instead. For participants who permanently discontinue study cream prior to the Week 8/EOT1 visit, the ET visit and evaluations should be conducted. If the ET visit coincides with a regular study visit, then the respective ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET page in the eCRF. If the decision to permanently discontinue study cream does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the ET procedures completed.

The end of treatment for the LTS period, and hence also the whole study (EOT2), coincides with the Week 52 visit. A participant who completes the Week 52/EOT2 visit will have reached the end of treatment with study cream. For participants who permanently discontinue study cream during the LTS period and prior to the Week 52/EOT2 visit, the ET visit and evaluations should be conducted. If the ET visit coincides with a regular study visit, then the respective ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET page in the eCRF. If the decision to permanently discontinue study cream 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.

8.8. Follow-Up

8.8.1. Safety Follow-Up

All participants will have a safety follow-up visit 30-37 days following the end of treatment (Week 52/EOT2 or ET) to evaluate safety and disease control parameters. One exception to this would be for participants in the LTS period who have been in an observation/no treatment cycle with a total IGA score of 0 (clear) from Week 48 or earlier until Week 52; for such participants, the Week 52/EOT2 visit will also count as the safety follow-up visit.

Adverse events and SAEs must be followed up until 1) at least 30 days after the last application of study cream or 2) 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, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study cream application are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study cream (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent/assent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

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

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

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study cream: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study cream as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and 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 in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study cream application, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Once an AE is detected, it should be followed in the Adverse Events Form in the eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study cream, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

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

Investigators are not obligated to actively seek SAE information after conclusion of study participation (ie, after the safety follow-up visit or 30 days after the last application of study cream, whichever occurs later). If the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study cream or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study 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 drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

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

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

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

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form or Study Reference Manual for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study cream because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

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

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

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.

9.8. 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/assent.

9.9. Product Complaints

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

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

The investigator or 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.

9.10. Treatment of Excessive Use

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

10. STATISTICS

10.1. Sample Size Determination

Approximately 100 participants will be enrolled. The study is not powered for statistical comparison but instead is based on the evaluation of safety. This sample size will provide > 99% chance of detecting at least 1 AE of interest if the underlying AE rate is 5%, and therefore it is anticipated that sufficient data for safety investigation will be permitted. As this is an open-label study, all participants will be treated with ruxolitinib 1.5% cream.

10.2. Populations for Analyses

The populations for analysis are provided in Table 11.

Table 11: Populations for Analysis

Population	Description
FAS	The FAS will include all participants enrolled in the study who applied study cream at least once. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and all analyses of efficacy and safety data.
PK/hematology lab evaluable	The PK evaluable population will include all participants who applied study cream at least once and provided at least 1 postbaseline PK sample (1 PK measurement). The hematology lab evaluable population will include all participants who applied study cream at least once, provided the baseline hematology blood sample, and at least 1 postbaseline hematology blood sample (1 hematology measurement). The PK/hematology lab evaluable population will include all participants who are both PK evaluable and hematology lab evaluable.

10.3. Level of Significance

This is a safety study. No formal hypotheses will be tested; all efficacy analyses are exploratory.

10.4. Statistical Analyses

10.4.1. Primary Analysis

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 up to 30 days after the last application of study cream. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study cream application. Treatment-emergent AEs will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on CTCAE v5.0 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to study cream will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study cream, then the AE will be considered treatment-related. The incidence of TEAEs, treatment-related TEAEs, serious TEAEs, Grade 3 or higher TEAEs, and TEAEs leading to

study cream interruption or study discontinuation will also be tabulated. A summary of primary endpoint analyses is provided in Table 12.

Table 12: Summary of Primary Endpoint Analyses

Endpoint	Population	Treatment	Population-Level Summary Metric
Incidence of TEAEs, treatment-related TEAEs, serious TEAEs, Grade 3 or higher TEAEs	FAS	Ruxolitinib 1.5% BID cream	Rate of TEAEs
Incidence of TEAEs leading to study cream interruption or study discontinuation	FAS	Ruxolitinib 1.5% BID cream	Rate of TEAEs
Incidence of TEAEs summarized by Grades of AE	FAS	Ruxolitinib 1.5% BID cream	Rates of TEAEs

10.4.2. Secondary Analyses

10.4.2.1. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics.

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. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated.

10.4.2.2. Vital Signs

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

10.4.3. Pharmacokinetic Analyses

Descriptive analysis of PK concentration data will be performed by matrix (plasma and saliva), study period, and/or visit, using summary statistics such as, but not limited to, number of observations, mean, STD, minimum, median, maximum, geometric mean, geometric coefficient of variation, and/or empirical percentiles as deemed appropriate.

Additional summaries may also be generated by subgroups such as geographical region, age, %BSA treated, and/or disease severity indices at baseline, as deemed appropriate.

Table 13 summarizes all secondary endpoint analyses.

Table 13: Summary of Secondary Endpoint Analyses

Endpoint	Population	Treatment	Population-Level Summary Metric
Change from baseline in vital signs	FAS	Ruxolitinib 1.5% BID cream	Descriptive statistics and mean change from baseline
Change from baseline in laboratory values	FAS	Ruxolitinib 1.5% BID cream	Descriptive statistics and mean change from baseline
Height	FAS	Ruxolitinib 1.5% BID cream	Descriptive statistics
Weight	FAS	Ruxolitinib 1.5% BID cream	Descriptive statistics
PK concentration	PK evaluable	Ruxolitinib 1.5% BID cream	Descriptive statistics

10.4.4. Exploratory Efficacy Analyses

[redacted]

10.4.5. Exploratory Analysis of Relationship Between Hematology Laboratory Results and Trough Ruxolitinib Concentrations

Exploratory descriptive and/or graphical analyses, as deemed appropriate, will be performed on the relationships between clinical laboratory test results of select hematology parameters such as platelet count, MPV, hemoglobin, and neutrophil count and the trough ruxolitinib concentration by visit.

Graphical analyses will include line plots of the mean ± STD values of the laboratory test results (the measured value, the change from the baseline, and/or the percent change from the baseline) by visit grouped by the trough ruxolitinib concentration quartiles (or other ways of discretization) as deemed appropriate.

The distribution of ruxolitinib concentrations versus the incidences and/or grade of severity of clinical laboratory CTCAE abnormalities in these hematology endpoints will be explored by the means of box-whisker plots or other types of visualization, as deemed appropriate.

Additional grouping methods based on participant-level characteristics such as age, %BSA, and/or IGA, may also be attempted in these analyses, as deemed appropriate.

A summary of all exploratory endpoint analyses is provided in Table 14.

Table 14: Summary of Exploratory Endpoint Analyses

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

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

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

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

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

11.3. Data Quality Assurance

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

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

11.4. Data Privacy and Confidentiality of Study Records

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

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

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

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

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

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

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

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

11.7. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females 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 with childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Number of Study Participants

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

Study Visits

Remote Site Visit Guidelines:

The evolving situation of the pandemic may lead to further travel restrictions and isolation requirements that could impact the participant. Also, the investigator's benefit/risk assessment may determine it to be unsafe for participants to attend study visits at the investigational site. In such cases, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video calls). At a minimum, a review of AEs, concomitant medications, and study cream compliance must be completed. Periodic on-site visits should be conducted whenever feasible, in particular the critical on-site visits outlined below.
- No investigator-assessed efficacy evaluations (ie, %BSA, IGA, or EASI) can be performed via telemedicine (video call or phone call).
- Laboratory sampling: No off-site laboratory sampling will be allowed.

Critical On-Site Visits:

The visits outlined below **must be performed in person** in order for the investigator to assess the participant's eligibility for the CT (screening and baseline) and LTS (Week 8) periods, and the participant's continued eligibility throughout the LTS period, even if the date that the participant eventually comes into the clinic deviates from the visit window.

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

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

- Screening
- Day 1 (Baseline)
- Week 8

During the LTS period, the participant may not miss consecutive on-site visits. For example, if the pandemic necessitates the participant to have a remote visit for Week 20, they could not also have a remote visit for Week 28. In addition, if a scheduled site visit is missed, if possible, the participant is encouraged to return to the clinic for an unscheduled visit prior to the next regularly scheduled Protocol-defined visit.

Investigational Medicinal Product Dispensing and Distribution

In order to ensure the continuity of providing their participants' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply study cream via shipment to participants.

If the participant cannot attend a visit at the study site, adequate supplies of study cream determined by the investigator can be shipped to the participant by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant.

The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits may be postponed due to documented COVID-19–related reasons; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, e-mails, video visits) with the sites to get information on trial progress, subject status, and information on issue resolution. The study monitor may remotely review data entered into electronic systems such as the EDC for accuracy and completeness. If allowed by local regulations, remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

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

Other Considerations

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of participants for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the

study investigator or institution, will reimburse the local physician for the tests/procedures conducted outside of the standard of care.

- In case of need, participants may refer to the local health care provider. Participants will be requested to obtain certified copies of the source data at the local health facility with the outcome of the contact and provide those to the investigator for appropriate oversight. The investigator/delegate will be requested to enter any relevant information into the EDC.
- Should COVID-19–related restrictions be localized and have an effect on a limited number of sites, the affected sites may utilize direct contracting of third parties to support continuous study conduct (eg, home nursing services, couriers, etc).

Reimbursement of Extraordinary Expenses

The sponsor will arrange to reimburse participants for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [nearby] laboratory tests).

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	30 NOV 2022

Amendment 1 (30 NOV 2022)

Overall Rationale for the Amendment

The primary purpose of this amendment is to clarify that Day 1 serum chemistry and hematology testing will be performed only if the screening laboratory test date is more than 2 weeks before Day 1. Additional changes and clarifications are summarized below.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Continuous Treatment Period; Table 4: Schedule of Activities: Long-Term Safety Period); Section 6.1.1, Study Treatment Application Guidance; Section 8.4, Pharmacokinetic Assessments (Table 10: Pharmacokinetic Blood and Saliva Sample Timing)**

   Description of change: Removed the requirement for all morning study cream applications to be performed at the site, and revised to allow participants to apply either of the 2 daily doses at the site after Day 1.

   Rationale for change: To allow flexibility in appointment time and to ease the burden on the participant and/or legal guardian.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Continuous Treatment Period); Section 8.3.5, Laboratory Assessments**

   Description of change: Updated to clarify that Day 1 testing for serum chemistries and hematology will only be performed if the interval between Day 1 and the date of the screening laboratory tests is great than 2 weeks.

   Rationale for change: To clarify when Day 1 testing is required.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Continuous Treatment Period; Table 4: Schedule of Activities: Long-Term Safety Period)**

   Description of change: Added an assessment for Itch NRS eDiary compliance.

   Rationale for change: To improve compliance of Itch NRS eDiary assessments.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Continuous Treatment Period); Section 8.4, Pharmacokinetic Assessments (Table 10: Pharmacokinetic Blood and Saliva Sample Timing)**

   Description of change: Revised the timing of the PK blood draw from morning to any time prior to study drug application but at least 4 hours after the previous application of study cream. Also, provided guidance on blood draws from treated areas if no other acceptable blood draw areas are available.

   Rationale for change: To decrease participant burden by allowing flexibility in the appointment time and minimize missed PK assessments.

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

   Description of change: Revised the exploratory endpoints for the evaluation of efficacy of ruxolitinib cream in adolescents with AD. Removed the Itch NRS score at each postbaseline visit, and add measurement timing for EASI scores, itch scores, and ITCH4.

   Rationale for change: To include the analysis of EASI scores and also the daily itch and Itch NRS responses at each postbaseline visit.

6. **Section 5.2, Exclusion Criteria (Criterion 12)**

   Description of change: Deleted the exclusion criterion regarding the inability to draw blood for PK from any nonlesional areas.

   Rationale for change: To allow for drawing blood from a treated area provided the study cream is not applied at that area during the previous application.

7. **Section 6.2, Preparation, Handling, and Accountability**

   Description of change: Revised study cream accountability at the conclusion of the study to reflect the process for handling remaining study cream for destruction at the site, or if local procedures do not allow on-site destruction, then shipment back to the sponsor is allowed.

   Rationale for change: To reflect the current procedure for sample accountability following completion of the study.

8. **Section 6.6, Concomitant Medications and Procedures**

   Description of change: Clarified the timeframes to be followed for recording in the eCRF for non-AD medications and treatments and for AD medications and treatments.

   Rationale for change: To allow collection of prior AD medications and treatments for a 12-month period.

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

   Description of change: Updated to allow the short-term use of systemic corticosteroids to treat acute AEs (eg, asthma) during the LTS period.

   Rationale for change: To allow for short-term treatment of a concomitant illness which has no impact on safety or efficacy.

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

    Description of change: Added acceptable forms of documentation that can be used to collect prior medical history for the use of topical prescription treatments or when those treatments were not advisable.

    Rationale for change: To provide guidance to the sites on the acceptable documentation for prior AD medical history.

11. **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.

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Approval Task	[redacted] Approver [redacted] Biostatistics 30-Nov-2022 22:58:30 GMT+0000

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