Official Title: A Phase 2, Efficacy and Safety Study of Ruxolitinib Cream in Participants with Facial and/or Neck Atopic Dermatitis Involvement

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Clinical Study Protocol

INCB 18424-215

A Phase 2, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Facial and/or Neck Atopic Dermatitis Involvement

Product:	**Ruxolitinib cream (INCB018424)**
IND Number:	[redacted]
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**19 MAY 2021**
Protocol Amendment 1:	**28 JUL 2021**
Protocol Amendment 2:	**04 AUG 2022**

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

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-215 Protocol Amendment 2 (dated 04 AUG 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)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
ClinRO	clinician-reported outcome
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DB	double-blind
DCT	decentralized trial
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI75	≥ 75% improvement in EASI score
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FTU	fingertip units
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy

Abbreviations and Special Terms	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment Treatment Success
IRB	institutional review board
IRT	interactive response technology
Itch NRS	Itch Numerical Rating Scale
ITT	intent-to-treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NCI	National Cancer Institute
OL	open-label
PDE4	phosphodiesterase-4
[redacted]	[redacted]
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	ultraviolet
VC	vehicle-controlled
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Facial and/or Neck Atopic Dermatitis Involvement

Protocol Number: INCB 18424-215

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 establish the efficacy of ruxolitinib cream in participants with AD on the face and/or neck.	Proportion of participants who achieve an EASI75 of the head and neck region at Week 4.
Secondary	
To further assess efficacy of ruxolitinib cream for the treatment of AD on the face, neck, and other body areas.	• Proportion of participants who achieve an EASI75 of the head and neck region at Weeks 2 and 8. • Proportion of participants who achieve an overall EASI75 at Weeks 2, 4, and 8.
To assess the safety and tolerability of ruxolitinib in participants with AD on the face and/or neck.	The type, frequency, and severity of AEs, including the evaluation of vital signs.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Treatment of patients with facial atopic dermatitis
Population	Male and female participants aged 12 to 70 years who have been diagnosed with AD for at least 6 months and present with active eczematous changes on the face and/or neck, who have an overall and face and/or neck IGA score of 2 or 3 at screening and baseline, and who have AD affecting ≥ 0.5% of the total BSA on the face and/or neck (excluding scalp). Participants with active AD lesions on their face and/or neck (fulfilling the % BSA criterion) who also have AD on other body areas (excluding the scalp) may be included if their total BSA involvement is ≤ 20%.
Number of Participants	Approximately 75 participants will be randomized 2:1 between 2 treatment groups. The participants will be stratified by face and/or neck IGA score at screening (IGA 2 or 3). Participants with a screening face and/or neck IGA score of 2 will constitute approximately 25% of the overall study population.

Table 2: Key Study Design Elements (Continued)

Study Design	Decentralized, randomized, 4-week, DB VC period followed by a 4-week, OL period and a 30-day, post-treatment, safety follow-up visit.
Estimated Duration of Study Participation	Estimated total duration of participation is approximately 17 weeks, including up to 5 weeks for screening, 4 weeks of DB treatment, 4 weeks of OL treatment, and 30 days for safety follow-up.
DSMB/DMC	No
Coordinating Principal Investigator	NA (1 site)

Treatment Groups and Duration:

Eligible participants will be randomized 2:1 to ruxolitinib cream 1.5% or vehicle cream BID and stratified by the face and/or neck IGA score (2 vs 3) measured at screening. Participants will apply blinded study drug starting at baseline (Day 1) through Week 4. Participants will then enter the OL period during which they will apply ruxolitinib 1.5% cream BID from Week 4 through Week 8.

The study design schema is presented in Figure 1 and the SoA is detailed in Table 3. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

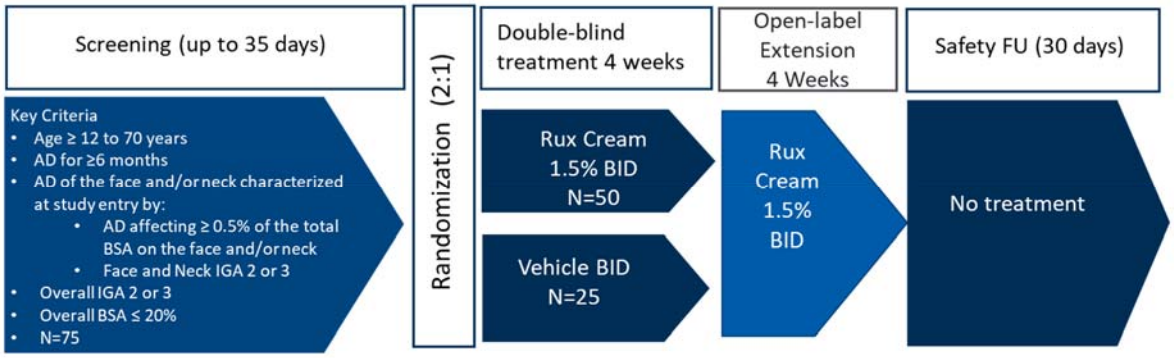

Table 3: Schedule of Activities

Visit Day (Range)	Screening Period		DB VC Period			Open-Label Period	Safety Follow-Up	Notes
	Screening Days −35 to −1	Randomization	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d) (EOT 1)	Week 8 (± 3 d) (EOT 2)	30 Days (+ 3 d) After Last Dose	
Administrative procedures								
Informed consent (including assent; electronic)	X							See Section 8.1.1. Consent is a separate virtual visit ahead of screening.
Contact IRT		X	X		X	X		See Section 8.1.3.
Inclusion/exclusion criteria review	X	X						See Section 5.
Demography and medical and disease history	X							See Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X	X	X	See Section 6.6.
Apply study drug			X					Study drug will be applied BID from Day 1 through Week 8. See Section 6.
Medication eDiary			X*	X	X	X		*Instructions for medication eDiary will be reviewed on Day 1 visit. Medication diary will be completed from the first application of study drug in the VC period through the end of the OL period.
Assess eDiary and study drug compliance			X*	X	X	X		*Itch NRS eDiary compliance will be assessed at baseline.
Collect study drug					X	X		Mobile healthcare provider will arrange for return of study drug to depot.
[redacted]								

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening Period		DB VC Period			Open-Label Period	Safety Follow-Up	Notes
	Screening Days −35 to −1	Randomization	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d) (EOT 1)	Week 8 (± 3 d) (EOT 2)	30 Days (+ 3 d) After Last Dose	
Safety assessments								
AE assessment	X		X	X	X	X	X	See Section 9.
Vital signs/body weight/height	X		X	X	X	X	X	Height and weight at screening only (see Section 8.5.2).
Efficacy assessments								
Full body photography	X		X	X	X	X	X	See Section 8.2.1.
EASI score Head and neck Overall	X		X	X	X	X	X	See Section 8.2.2.
[redacted]								
%BSA Face and/or neck Overall	X		X*	X	X	X	X	See Section 8.2.4. *BSA to be assessed independently in real time during the baseline visit before dose administration (see Section 7.2).
Laboratory assessments								
Chemistry	X							See Table 7.
Hematology	X							See Table 7.
Serology	X							See Section 8.5.3.2.
FSH	X							Women of nonchildbearing potential only (see Section 8.5.3.1)
Serum pregnancy test	X							WOCBP only (see Section 8.5.3.1).
Urine pregnancy test			X		X	X	X	WOCBP only (see Section 8.5.3.1).

Note: Visits will be a combination of telemedicine and mobile healthcare provider visits.

2. INTRODUCTION

2.1. Background

Atopic dermatitis is a chronic, recurring, inflammatory skin disease characterized by significant pruritus, epidermal barrier disruption, and an impaired innate immune response that results in enhanced penetration of allergens and pathogens through the skin (De Benedetto et al 2011, Eichenfield et al 2014a, Gittler et al 2012, Howell 2007, Lio et al 2014, Palmer et al 2006). Worldwide, up to 25% of children and up to 12% of adults have AD (Eichenfield et al 2014a, Hanifin et al 2007, Harrop et al 2007, Rönmark et al 2012). Atopic dermatitis is the most common disease of the skin, and its incidence in industrialized countries appears to be increasing (Ellis et al 2002, Laughter et al 2021). In the US, the prevalence of AD in adults is estimated to be 7.2% (Chiesa Fuxench et al 2019, Silverberg et al 2015). It is not clear how many adolescents suffer from AD, as this age subgroup is usually not reported separately from the overall pediatric population. However, one study (Shaw et al 2011) gave the estimated frequency rate of AD in adolescents 13 to 17 years of age as 8.6%. Fewer than 20% of adults with AD develop the disease in adulthood (Ozkaya 2005), which indicates the vast majority of adult patients with AD have never grown out of their childhood/adolescent affliction (Williams and Strachan 1998).

According to the recent Global Burden of Disease project, AD is 1 of the 50 most prevalent diseases worldwide (Hay et al 2014), and it has the highest disease burden among skin diseases as measured by disability-adjusted life years (Laughter et al 2021). Atopic dermatitis is associated with significantly diminished quality-of-life owing in large part to chronic itch and associated sleep disturbances (Silverberg et al 2015, Silverberg et al 2018b, Zuberbier et al 2006). Chronic itch has been shown to have profound economic, educational, and occupational impacts on patients with AD.

Although not life-threatening in and of itself, AD is associated with numerous allergic/atopic comorbidities, some of which may be life-threatening (Eichenfield et al 2014a, Gustafsson et al 2000, Spergel 2010). In addition, an increasing number of publications have stipulated that AD may be associated with other systemic and non–skin-related conditions, including psychiatric and metabolic complications (Deckert et al 2014, Kauppi et al 2019, Paller et al 2018, Shalom et al 2019, Silverberg et al 2011, Silverberg et al 2015, Silverberg et al 2018a, Strom et al 2016, Yaghmaie et al 2013). It may also be a risk factor for cardiovascular diseases (Ivert et al 2019, Standl et al 2017). These comorbid conditions may be related to the chronic pruritus experienced by patients.

The management of AD is guided by many factors, including severity of flares, extent of disease, symptoms, and impact on quality of life. Basic management (ie, education of patients about skin hydration, the use of emollients, and avoidance of factors that worsen the disease) is used in patients with mild disease, and topical anti-inflammatory medications are added when nonpharmacologic interventions are not sufficient to control inflammation and itching. In patients with severe or recalcitrant disease, phototherapy and/or systemic therapies may be added.

Topical agents are the mainstay of AD treatment. The current prescription topical anti-inflammatory medication armamentarium includes topical corticosteroids, topical

calcineurin inhibitors, and a PDE-4 inhibitor, crisaborole ointment (Eucrisa® 2020). The former classes of medications are effective in treating signs (erythema, induration/papulation, and oozing/crusting) and symptoms of AD but may be associated with adverse effects.

Topical corticosteroids of any potency may cause skin atrophy, purpura, telangiectasia, striae, focal hypertrichosis, and acneiform or rosacea-like eruptions (Eichenfield et al 2014b). Topical corticosteroids may also cause hypothalamic-pituitary-adrenal axis suppression. The risk of cutaneous adverse effects increases with higher-potency agents, occlusion, use on thinner skin, and advanced age, and the risk of systemic side effects increases with prolonged continuous use.

The topical calcineurin inhibitors, tacrolimus ointment (Protopic® 0.03% and 0.1% ointment) and pimecrolimus cream (Elidel® 1% cream), are used in the second-line setting for their steroid-sparing properties. Skin burning and pain are common application-site reactions following application of topical calcineurin inhibitors (Eichenfield et al 2014b, Elidel 2020, Protopic 2019). In addition, topical calcineurin inhibitors carry a boxed warning that rare cases of malignancy (eg, skin cancer and lymphoma) have been reported in patients treated with these agents, although a causal relationship has not been established.

To minimize adverse effects, the use of topical corticosteroids on sensitive skin areas (eg, the face) and the long-term use of topical corticosteroids and topical calcineurin inhibitors are not recommended (Eichenfield et al 2014b).

Crisaborole ointment, which is indicated for patients 3 months of age and older with mild to moderate AD, has no such safety limitations but was shown to have modest efficacy (Eucrisa 2020).

Thus, there remains a significant medical need for topical therapies that provide both rapid and long-term control of the signs and symptoms of the disease, specifically on sensitive skin areas such as the face and neck.

2.2. Study Rationale

This study is designed to further evaluate the efficacy and safety of ruxolitinib cream in individuals with AD affecting at least 0.5% of the total BSA on the face and/or neck.

Ruxolitinib cream is a potent inhibitor of JAK1 and JAK2 with dual anti-inflammatory and antipruritic properties and has been recently shown to be an effective and safe therapy for AD in patients ≥ 12 years of age (Kim et al 2020a, Kim et al 2020b, Papp et al 2020). Ruxolitinib 1.5% cream is approved by the FDA for the treatment of AD in nonimmunocompromised patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable (Opzelura™ 2021). Given its topical application, treatment of AD with ruxolitinib cream selectively targets the diseased skin and minimizes the chance of safety concerns associated with the systemic administration of JAK inhibitors.

2.2.1. Scientific Rationale for Study Design

Two Phase 3 pivotal studies (INCB 18424-303 and INCB 18424-304) demonstrated that ruxolitinib 1.5% cream BID was statistically significantly superior to vehicle after 8 weeks of treatment for the primary endpoint, IGA-TS (a score of 0 or 1 with ≥ 2 grade improvement from baseline), and key secondary endpoints, including a 75% improvement in the EASI and at least a 4-point improvement in the Itch NRS (Papp et al 2020). The 1.5% strength was also superior in

efficacy to the 0.75% strength with nondifferentiating safety profiles of both regimens. The purpose of this study is to further investigate and confirm the efficacy and safety of ruxolitinib cream (1.5%) when applied to affected areas on the face and neck.

This study will be a fully DCT. The benefits of a DCT include enhancing the participant's experience, minimizing day-to day disruption, eliminating travel burden, potentially increasing participant diversity, and improving participant retention. All visits will be conducted remotely via telemedicine (telephone and/or video) or in-home visits by a trained mobile healthcare provider. Efficacy assessments will be performed by an investigator/rater (dermatologist; central reader) using high-quality digital photographs. A validation study demonstrated excellent agreement between assessment of AD severity using EASI, SCORAD, IGA, and BSA during in-home visits and via digital photographs (Hughes et al 2019).

This study will enroll both male and female participants ≥ 12 years of age with both an overall and a face and/or neck IGA score of 2 or 3 and AD affecting at least 0.5% of the total BSA on the face or neck. Participants in the Phase 3 studies had AD involvement of 3% to 20% BSA (excluding the scalp) and an IGA score of 2 to 3 at baseline. Although approximately 39% of participants with AD in the Phase 3 studies reported prior facial involvement, the efficacy assessments in these studies (eg, IGA-TS and EASI) were based on the all (total) AD-affected areas. The study population for this trial will be similar to the Phase 3 study population with the exception that in this study, all participants must have AD lesions on the face and/or neck region involving at least 0.5% of their total BSA in that area.

The clinical endpoints in the study will be similar to those in the Phase 3 studies, except the primary endpoint will be the proportion of individuals who achieve EASI75 in the head and neck region [redacted] will be included as secondary [redacted] endpoints.

The selection of a vehicle control for 4 weeks is based on the chronic, relapsing nature of AD and the low risk to participants of using a vehicle for 4 weeks. Moreover, this duration of treatment is anticipated to be sufficient for the evaluation of treatment effect in this specific body location. The 4-week, OL extension will allow participants who were randomized to vehicle the ability to receive treatment and the participants randomized to active to continue treatment if clearance (IGA = 0) was not achieved in 4 weeks. It is also expected to decrease dropout rates in the vehicle arm by offering an incentive to participants to remain in the study beyond the initial 4-week, DB VC period.

In the Phase 3 AD studies, efficacy was seen as early as the first postbaseline visit, Week 2, and continued through Week 8. The assessment of efficacy at 4 weeks is supported by the data from the Phase 3 studies.

Based on the low bioavailability of ruxolitinib cream following twice-daily applications for up to 8 weeks in individuals with AD and the absence of clinically meaningful laboratory findings (hematology and chemistry) in the Phase 3 studies that could be attributed to the therapy with ruxolitinib cream, laboratory tests will be collected at screening only.

2.2.2. Justification for Dose

Data from the Phase 3 pivotal studies in participants ≥ 12 years of age with AD were the basis for the selection of the 1.5% BID regimen in this study. Overall, ruxolitinib 1.5% cream was found to be more efficacious than its 0.75% strength, while the safety and tolerability profiles of both treatment arms were comparable and nondifferentiating. Of note, the Phase 3 efficacy and safety findings were on par and thus fully confirmatory to the outcomes of the earlier Phase 2 dose range-finding study.

The efficacy and safety outcomes from the pivotal Phase 3 studies are summarized below:

- Ruxolitinib 1.5% cream BID was statistically significantly superior to the vehicle at Week 8 for IGA-TS, EASI75, and ≥ 4-point improvement in Itch NRS score.
- The antipruritic effect of ruxolitinib cream 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 drug).
- The consistent treatment effects of ruxolitinib 1.5% cream on IGA-TS, EASI75, and Itch NRS score were also observed across all subgroups irrespective of demographic and baseline characteristics, which supports the generalizability of benefit to patients aged 12 years and older who may use ruxolitinib cream.
- Safety data from the Phase 3 VC AD studies demonstrate that ruxolitinib 1.5% cream applied BID continuously for 8 weeks in adolescent and adult participants with AD was safe and well-tolerated.

Based on the Phase 3 data, the proposed treatment regimen for the current study is ruxolitinib 1.5% cream BID.

2.3. Benefit/Risk Assessment

Safety data on the use of ruxolitinib cream are available from 2350 participants who applied ruxolitinib cream across multiple indications. In AD, the safety database consists of 1463 participants who applied ruxolitinib cream, evaluated in clinical studies. No safety concerns for ruxolitinib's strength were identified in the 1463 participants with AD who applied ruxolitinib cream. In addition, ruxolitinib cream was also found to be well-tolerated and safe in participants with extensive AD lesions, in other words, those involving at least 25% of the participant's total BSA (maximum use trial; INCB 18424-103).

In summary, ruxolitinib cream did not present with any clinically meaningful tolerability issues, including its use on the face and/or neck area, or concerning safety findings.

The most commonly reported TEAEs while receiving ruxolitinib treatment were upper respiratory tract infection in 104 participants (7.1%), nasopharyngitis in 103 participants (7.0%), and headache in 39 participants (2.7%); all other TEAEs were reported in ≤ 2% of participants. All SAEs were reported for 1 participant each (0.1%).

The majority of participants had good local tolerability with ruxolitinib cream use. Few application site reactions were reported: application site pain (6 participants; 0.4%); application site pruritus (4 participants; 0.3%); application site erythema (2 participants; 0.1%); and application site folliculitis, application site irritation, application site papules, application site

paresthesia, and application site urticaria (1 participant each; 0.1%). All application site reactions among participants with AD were Grade 1 or 2 in severity.

Local tolerability studies (INCB 18424-105, INCB 18424-107, and INCB 18424-108) in healthy participants demonstrated that ruxolitinib 1.5% cream was not phototoxic and did not induce photosensitization. However, due to the theoretical risk of skin reaction when exposure to ruxolitinib is combined with sun exposure, participants should be cautioned to avoid prolonged exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc), and when outdoors, should be advised to wear loose-fitting clothing that protects the treated area from the sun.

Current approved topical therapies for AD remain suboptimal due to their efficacy limitations and safety concerns, particularly for long-term use, specifically for sensitive areas such as the face and neck. Based on the Phase 3 data, participants in this trial may benefit from a rapid reduction in itch and the inflammatory signs of AD with ruxolitinib cream, which is generally safe and well-tolerated. 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 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib cream in participants with AD on the face and/or neck.	Proportion of participants who achieve an EASI75 of the head and neck region at Week 4.
Secondary	
To further assess efficacy of ruxolitinib cream for the treatment of AD on the face, neck, and other body areas.	• Proportion of participants who achieve an EASI75 of the head and neck region at Weeks 2 and 8. • Proportion of participants who achieve an overall EASI75 at Weeks 2, 4, and 8.
To assess the safety and tolerability of ruxolitinib in participants with AD on the face and/or neck.	The type, frequency, and severity of AEs, including the evaluation of vital signs.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a decentralized, randomized, DB, VC study with a 4-week, OL period in adolescent and adult participants with AD (including AD on the face and/or neck) eligible for topical therapy. This study will be conducted through a single, stand-alone, virtual site in the US. All study visits will be conducted in the participant's home with the assistance of a mobile healthcare provider and investigator or designee present through telemedicine (telephone and/or video visits).

Prospective participants who are assessed as preliminarily eligible will be emailed a link to a secure portal to review the electronic version of the IRB-approved consent with the investigator or designee during a telemedicine visit. If the individual agrees to participate, they will provide a handwritten signature executed to an electronic record. The investigator will counter sign the ICF/assent in the same manner. The participant will be able to download a copy of the ICF/assent, or the site can provide a copy via email. The informed consent process will be documented by the investigator and maintained as part of the participant's source documentation.

Following consent/assent, sample collection kits, instructions, and other study materials will be provided via direct-to-participant shipments. Once eligibility is confirmed, the participant will be randomized during the screening period to allow time for the study drug to be shipped to the participant in time for the first dose administration on Day 1. Prior to application of the first dose of study drug, the investigator will confirm participant can continue with study participation on baseline/Day 1.

Participants will be randomized 2:1 to blinded treatment with ruxolitinib cream 1.5% BID or vehicle cream BID with stratification by screening face and/or neck IGA score (IGA 2 or 3). Participants with a screening face and/or neck IGA score of 2 will constitute approximately 25% of the overall study population.

During the 4-week, DB VC period, participants will apply study treatment BID to all areas identified for treatment at the baseline visit even if the AD begins to improve and lesions decrease in size. The mobile healthcare provider will take comprehensive photographs for the investigator to assess the AD-affected areas for the clinician-reported assessments detailed in Table 3. After all the Week 4 study assessments are complete, participants who complete the Week 4 visit with no safety concerns will continue into the 4-week, OL period and will apply ruxolitinib cream 1.5% BID only to affected areas.

Throughout the study, participants who develop additional areas of AD may treat those areas with approval from the investigator, as long as the total treated BSA does not exceed 20% and there are no safety concerns regarding the additional application of study drug. Approval to treat additional areas will occur via telemedicine visits.

If AD lesions clear during the 4-week, OL period, participants will stop treatment applications 3 days after the lesions have disappeared and record the dates of these events in their diaries. If the AD lesions recur, participants may restart treatment at home at the first sign of recurrence and record the date of study drug administration.

At Week 4, efficacy (the primary endpoint of the study) will be evaluated as the proportion of participants who achieve an EASI75 of the head and neck region. Additional efficacy assessments and patient-reported outcomes will be conducted as outlined in the SoA (see Table 3).

Participants will be assessed for safety and tolerability throughout the study by monitoring the type, frequency, and severity of AEs and measuring vital signs (see Table 3).

Figure 1 presents the study design schema, and the SoA for the VC and OL periods is in Table 3.

4.2. Overall Study Duration

The study will begin when the first participant (or parent or guardian) signs the ICF (and, if needed, an assent form). The end of the study is defined as the date of the last visit of the last participant in the study or the date that the last participant has discontinued study drug 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 17 weeks as follows: up to 35 days in the screening period, 4 weeks in the DB VC period, 4 weeks in the OL period, and 30 (+ 3) days for follow-up after the last application of study drug.

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 if, for example, required by regulatory decision. 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. Ability to comprehend and willingness to sign a written ICF for the study or written informed consent of the parent(s) or legal guardian and written assent from the participant when applicable.

   Note: Adolescent participants who become legal adults during the study will be asked for their signed consent to continue the study.
2. Adolescents and adults aged 12 to 70 years.
3. Participants diagnosed with AD as defined by Hanifin and Rajka (1980) criteria based on patient-reported history and investigator assessment at study entry.
4. AD for a duration of at least 6 months.
5. Participants with an overall and a face and/or neck IGA score of 2 or 3 at screening.
6. Participants with AD affecting the following at screening:
   a. ≥ 0.5% of the total BSA on the face and/or neck
   b. Up to a total of 20% BSA (face and/or neck plus other body areas)
7. Participants with adequate venous access in areas unaffected by AD.
8. Participants who agree to discontinue all other agents used to treat AD from screening through the final follow-up visit.
9. 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 dose of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Female participants who are WOCBP must have a negative serum pregnancy test at screening, a negative urine pregnancy test before the first dose on Day 1, and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study drug and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   c. A female participant not considered to be of childbearing potential as defined in Appendix A is eligible.

5.2. Exclusion Criteria

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

1. Participants who have an unstable course of AD (spontaneously improving or rapidly deteriorating) as determined by the investigator over the previous 4 weeks prior to baseline.
2. Participants with concurrent conditions and history of other diseases as follows:
    a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich Syndrome).
    b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit.
    c. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) within 1 week before the baseline visit.
    d. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton's 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. Other types of eczema.
    f. Chronic asthma requiring more than 880 µg/day of inhaled budesonide or equivalent high-dose of other inhaled corticosteroids.
3. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
4. Participants using any of the following treatments within the indicated washout period before the baseline visit:
    a. 5 half-lives or 12 weeks, whichever is longer – for biologic agents (eg, dupilumab).
    b. 4 weeks – cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
    c. 4 weeks – systemic corticosteroids or adrenocorticotropic hormone analogs.
    d. 2 weeks – immunizations; sedating antihistamines unless on long-term stable regimen (nonsedating antihistamines are permitted).
    e. 1 week – use of topical treatments for AD (other than bland emollients) such as topical antipruritics (eg, doxepin cream), corticosteroids, calcineurin inhibitors, PDE4 inhibitors, coal tar (shampoo), topical antibiotics, antibacterial cleansing body wash/soap. Note: diluted sodium hypochlorite "bleach" baths are allowed as long as they do not exceed 2 baths per week.
5. Previous treatment with systemic or topical JAK inhibitors (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).
6. Ultraviolet light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, sunlight or tanning booth) within 4 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.

7. Any of the following clinical laboratory test results at screening:
    a. Removed in Protocol Amendment 1.
    b. Removed in Protocol Amendment 1.
    c. Liver function tests:
        - AST or ALT ≥ 2.5 × ULN.
        - Total bilirubin > 1.5 × ULN unless Gilbert's Syndrome.
    d. Positive serology test result for HIV antibody.
    e. Cytopenias, defined as follows:
        - Hemoglobin < 10 g/dL
        - Absolute neutrophil count < 1000/µL
        - Platelet count < 100,000/µL
    f. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease equation).
    g. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.
8. Evidence of HBV or HCV infection or risk of reactivation. Participants cannot be positive for HBsAg, anti-HBcAb, or HCVAb, except in the cases below:
    - Participants with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody (HBsAb) against HBsAg as the only evidence of prior exposure may participate in the study.
    - Participants with a history of HCV infection who are antibody-positive and have successfully completed treatment > 12 weeks before screening, and have no detectable HCV RNA, are allowed in the study.
9. Participants who are pregnant (or who are considering pregnancy) or lactating.
10. History of alcoholism or drug addiction within 1 year before screening, or current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the administration schedule and study assessments.
11. Removed in Protocol Amendment 1.
12. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication or current enrollment in another investigational drug study.
13. Participants who, in the opinion of the investigator, are unable or unwilling or unlikely to comply with the administration schedule and study evaluations.

5.3. Lifestyle Considerations

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

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

Participants should abstain from physical activity that can cause significant sweating for 2 hours following study drug application. Study drug should be applied at least 2 hours after shaving.

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

The participant's living environment should be suitable for study participation, eg having appropriate place for televisits, with internet connection. In addition, participant's activities are to be compatible with visit schedule over the 3 months of study participation.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, completed the screening visit, 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 > 35 days after the initial screening) and be assigned a new participant number.

Participants who have been randomized but terminated early from the study prior to dose administration are not screen failures. However, upon sponsor approval, they may be invited for a second participation in the study by reconsenting and rescreening. They will be assigned a new participant number.

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Information regarding study drug and administration is provided in Table 5. Participants will record study drug administration in a daily diary.

Table 5: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name:	Ruxolitinib	Vehicle
Mechanism of action:	JAK1/2 inhibitor	NA
Dosage formulation:	Cream	Cream
Unit dose strength(s)/dosage level(s):	1.5%	NA
Route of administration:	Topical	Topical
Administration instructions:	DB VC period: Apply a thin film to affected areas identified at baseline in the morning and at least 1 hour before bedtime for 4 weeks. OL period: Apply a thin film to affected areas only in the morning and at least 1 hour before bedtime as needed for 4 weeks.	
Packaging and labeling	Ruxolitinib and vehicle will be provided in 60-g tubes. Tubes will include labeling in the local language and will comply with the legal requirements of the country.	
Storage:	Ambient (15°C-30°C/59°F-86°F)	
Status of treatment in participating countries:	Investigational	

At randomization after eligibility has been confirmed, the %BSA assessed at screening will be used by the IRT system to calculate the number of tubes of study drug to be dispensed for initial supply.

During the DB VC period, all areas identified at the baseline visit should continue to be treated through the end of the period (at Week 4) even if the area begins to improve or the AD resolves completely, unless the participant meets criteria for stopping study drug.

During the OL period, starting at the Week 4 visit, only areas with active disease need to be treated. If the lesions clear, participants should continue to apply study drug for an additional 3 days to the areas of the body where lesions were last present. After 3 days of applying study drug to area where the lesions resolved, treatment should be discontinued. If this 3-day window is during a study visit and the IGA score is 0, as assessed by the investigator, treatment is to be stopped. The date of the study visit will be recorded as the treatment cycle end date. If a lesion recurs, then treatment should be resumed at the first sign of recurrence. The start and end dates of treatment applications and/or interruptions will be captured by the participant in the electronic medication diary.

At any time during the study, participants who develop additional areas of AD may treat these additional areas with approval of the investigator as long as the total treated BSA does not exceed 20% and there are no safety concerns. Approval to treat additional areas can occur via telemedicine visit. The new %BSA should be entered into the CRF. The participant should be discontinued if total treated BSA is >20%.

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

6.1.1. Study Drug Application

Participants should remove study drug from the tube in FTUs until all affected areas are covered by a thin even film. The recommended maximum amount of the study drug per application should be calculated as: total FTUs = total %BSA involvement / 2. For example, a participant with 3% total BSA would apply a total of 1.5 FTUs.

One FTU is the amount of topical study drug that is squeezed out from the tube along the participant's fingertip. A fingertip is from the very end (tip) of the finger to the first crease in the finger. One FTU is enough to apply a thin film of study drug to an area of skin twice the size of the flat of a participant's hand with the fingers together (or ~2% BSA).

6.2. Preparation, Handling, and Accountability

The investigator or designee, must confirm appropriate temperature conditions have been maintained during transit or storage for all study drug received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment. Study treatment will be shipped directly to the participant who will received appropriate instruction on how to handle and store before the next visit. All study treatment must be stored in accordance with the labeled storage conditions and should be stored in a location out of the reach of children.

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

- Delivery of study drug to the participants.
- Inventory of study drug for the individual participants.
- Participant use of the study drug, including tube counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants or remote healthcare worker.

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system (see Section 8.1.3). The system will assign in a 2:1 ratio, stratified by screening face and/or neck IGA score (2 or 3). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the IRT will be provided to the site. Full details will be provided in the IRT Manual.

Study drug will be shipped directly to the participant once study eligibility is confirmed.

Participants, investigators, and the sponsor will remain blinded to each participant's treatment assignment during the DB VC period. Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.6 and refer to the IRT Manual).

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance will be assessed by the site staff for frequency of administration of study drug by reviewing the participants' diaries. Participants will also be questioned regarding study drug application technique, missed applications, and use of any additional topical or systemic prescriptions of other products or over-the-counter products. Compliance with study drug will be evaluated based on the participant's adherence to the application regimen (evaluation of actual number vs prescribed number of applications), documented by the site staff, and monitored by the sponsor/designee.

Qualified clinical staff will review the diary entries for compliance. Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the prescribed number of applications during participation in the treatment portion of the study. Participants who are noncompliant during the DB or OL periods will be reinstructed by the investigator (or designee), and the sponsor should be consulted by the investigator for repeated non-compliance and 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 visit and subsequent study visits, the amount of

study drug to be applied is to be determined by weighing a tube before and after the participant applies a thin film of study drug to the affected areas.

6.5. Dose Modifications

No dose modifications are allowed during the study. The only modifications to the treatment regimen are temporary or permanent discontinuation of the study drug. In some circumstances, it may be necessary to temporarily interrupt treatment with study drug as a result of AEs that have an unclear relationship to the study drug.

6.5.1. Criteria and Procedures for Application Interruptions of Study Drug

Individual decisions regarding interruptions due to an AE should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study drug and the participant's underlying condition. In addition to these guidance steps, safety concerns should be discussed with the sponsor (or representative) immediately upon occurrence or awareness.

6.5.2. Criteria for Permanent Discontinuation of Study Drug

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

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- A worsening of AD that requires treatment with a prohibited concomitant medication (see Section 6.6.3) or total BSA to be treated > 20%.
- A persistent AE requiring a delay of therapy for more than 14 days unless a greater delay has been approved by the sponsor.

See Section 7 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 12 weeks before the first dose of study treatment and through 30 days after the last application of study treatment will be recorded in the eCRF.

Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered more than 30 days after the last dose of study treatment should be recorded for SAEs until the SAE is no longer being followed. 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.
- If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide– or titanium oxide–based) with an SPF of at least 30 may be used at least 4 hours before and at least 2 hours after study drug application.
- Bathing during the study should be limited to once daily for no longer than 15 minutes and not within 2 hours following study drug 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.

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Participants may continue using sedating antihistaminic drugs as long as their use is part of a pre-existing and well-established regimen. There are no restrictions for use of nonsedating antihistamines.
- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant derived preparations) within 7 days before the baseline visit through the follow-up visit, unless deemed acceptable by the investigator.
- Use of any prescription medication (including immunizations, phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the follow-up visit, unless deemed acceptable by the investigator.
- Bleach baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
- Participants should not take baths or showers within 2 hours after study drug application.
- Participants should apply study drug at least 2 hours after shaving.
- Topical anti-infectives or other topical treatments applied to active AD lesions should not be used for at least 4 hours before and 2 hours after application of study drug.
- Inhalation therapy for bronchial asthma or chronic obstructive pulmonary disease with the dose of budesonide or other equivalent inhaled corticosteroids may not exceed 880 µg.

- Participants may continue to use makeup but may not change or introduce makeup within 4 weeks before baseline and throughout the study.

  Note: Makeup should not be used on affected areas within 30 minutes after application. All makeup should be removed at least 1 hour prior to study visits.

6.6.3. Prohibited Medications and Procedures

The following are not permitted during the study:

- Any investigational medication other than the study drug.
- Any topical or systemic JAK or TYK2 inhibitor other than ruxolitinib cream (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib, abrocitinib, brepocitinib).
- Systemic immunosuppressive or immunomodulating biologic drugs (eg, adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, brodalumab, ixekizumab, risankizumab, guselkumab, bimekizumab, iscalimab, bermekimab, rituximab, anakinra).
- Systemic immunosuppressive or immunomodulating small-molecule drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, dapsone, azathioprine).
- Topical corticosteroids, tacrolimus, pimecrolimus, and PDE4 inhibitors (Eucrisa).
- Other topical agents for AD (except bland emollients as noted in Section 6.6.1).
- Treatment known to affect the course of AD.
- Allergen immunotherapy.
- Phototherapy or tanning beds.
- Live or live-attenuated vaccination.

6.7. Treatment After the End of the Study

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Disease worsens to the point where the extent of affected area to be treated exceeds 20% BSA.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.2.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, after 2 consecutive study visits and reinforcement of study drug application by site staff, a participant's drug usage exceeds one 60-g tube every 4 days; a participant who again fails to meet compliance benchmarks at a subsequent visit may be considered for withdrawal from the study. The medical monitor should be consulted for instruction on handling the participant.
- If, during the course of the study, a participant is found not to have met eligibility criteria, the investigator, in collaboration with the medical monitor, will determine whether the participant should be discontinued from study treatment.
- If a participant is noncompliant with study procedures or study drug/treatment handling or administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant complete the follow-up visit. These visits are described in Table 3. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record (source document) and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities 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/efficacy assessments.

7.2. Participant Withdrawal From the Study

At the baseline visit (Day 1), a participant will be withdrawn from the study prior to receiving first dose of study drug if the following occur:

- Participant's overall and face/neck IGA score is 1 or 4 or
- Participant's BSA is < 0.5% of the total BSA on the face and/or neck or
- Participant's BSA is > a total of 20% BSA (face and/or neck plus other body areas)

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

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

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. If no visit is completed at time of withdrawal, the participant should return investigational product per sponsor's instructions.

7.3. Lost to Follow-Up

After consent is signed, a participant will be considered lost to follow-up if he/she is not able to attend for one scheduled visit and is unable to be contacted by the study site to reschedule, despite all efforts from site staff to contact.

The following actions must be taken if a participant fails to be available for a required telemedicine and in-home healthcare worker 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. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to be lost to follow-up and have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent/assent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.

  Note: Adolescent participants who become legal adults during the study will be asked for their signed consent to continue in the study and in the event of lack thereof, will be discontinued from further participation.
  - Informed consent/assent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF/assent must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent/assent that meets the applicable requirements and regulations for the country in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record (source document) must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF.
- 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 must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF/assent (if rescreened > 35 days after the initial screening) and must be assigned a new participant number.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF/assent and the day the participant is dosed in the study (Day 1). Screening may not exceed 35 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 35 days of Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before randomization. At the baseline visit (Day 1), a participant will be confirmed that they can continue with study participation (eg, meeting disease activity requirements regarding IGA and BSA, and prior and concomitant medication requirements) prior to the first administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine eligibility.

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the 2 letter country code (US), 3-digit site ID, and 3-digit participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted as detailed in Table 3 to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Notification and eDiary

Participants will be provided with a reminder notification for each visit. The reminder notification will indicate the date/time of the next visit and will also remind the participant that they should not apply their study drug within 1 hour of each visit.

An electronic study medication diary (eDiary) will be used by each participant in order to record their twice per day application of study drug. The completed eDiary will be reviewed during each of the participant's study visits and data uploaded as well as compliance with eDiary completion will be confirmed by the study staff.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

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

8.1.5.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

The investigator or designee will independently assess the ClinROs (EASI, [redacted]nd %BSA involvement) via the digital photographs. Rater performing the assessment will be distinct from the investigator conducting the televisit. If possible, the same rater should perform the assessment for the same participant at every visit. At the baseline visit, clinical assessments (eg, IGA, BSA) need to be completed during the visit prior to first study drug application.

8.2.1. Full-Body Photography

For the ClinRO assessments (EASI, [redacted]nd BSA), full body photographs will be captured by the mobile healthcare provider at the visits designated in Table 3. The photograph set will undergo a quality-control process to ensure photographs are of sufficient quality for ClinRO assessments. The rater (a dermatologist) will rate the participant's AD severity using the specified ClinRO assessments described in Sections 8.2.2, 8.2.3, and 8.2.4. The mobile healthcare provider will be trained to take a standard set of full-body photographs. A reference guide will be provided to the mobile nurse for photo capture during the remote visit. An investigator will provide oversight during the photography capture process to determine in real-time if the photographs obtained are of sufficient quality. Photographs not meeting the assessment standard will be retaken during the same session.

The investigator or designee will document in the eCRF the specific affected areas of the face (forehead, cheeks, chin, nose, eyelids, periocular, and mouth) and other body areas based on the photographs.

8.2.2. Eczema Area and Severity Index

Atopic dermatitis will be assessed as outlined in the SoA (see Table 3) using the EASI scoring system, which is a validated scoring system that grades the physical signs of AD to provide a measure of AD severity (ranging from 0 to 72). The EASI score for the head and neck region ranges from 0 to 7.2. 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.

8.2.3. Investigator's Global Assessment

The IGA is an overall eczema severity rating on a 0 to 4 scale that will be assessed overall and for the face and/or neck, during visits as detailed in Table 3. The severity strata are shown in Table 6.

Table 6: 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

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

8.2.4. Body Surface Area

At the visits designated in Table 3, the %BSA involvement on the face and/or neck and overall will be determined to the nearest 0.1%. Participants with AD affecting ≥ 0.5% of their total BSA on the face and/or neck at screening and baseline and up to a total 20% overall total BSA are eligible for the study.

8.2.5. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

[redacted]

[redacted]

8.5. Safety Assessments

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

8.5.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

8.5.2. Vital Signs

Vital signs, height, and weight will be measured as outlined in the SoA (see Table 3).

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. At screening, vital sign measurements should be obtained before blood collection for laboratory tests. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require study drug interruption or discontinuation.

8.5.3. Laboratory Assessments

See Table 7 for the list of clinical laboratory tests to be performed at screening. A central laboratory will perform all clinical laboratory assessments for safety (ie, chemistry, hematology assessments, and serology). 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). Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

Screening laboratory assessments must be performed within 35 days before Day 1. If performed more than 35 days before Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Day 1.

Table 7: Required Laboratory Analytes

Serum Chemistries	Hematology	Serology/Infection	Pregnancy Testing (Urine and Serum)
• Albumin • Alkaline phosphatase • Alanine aminotransferase • Aspartate aminotransferase • Blood urea nitrogen or urea • Creatine kinase • Creatinine • Glucose • Total bilirubin • Direct bilirubin (if total bilirubin is elevated above ULN)	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • WBC count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	• HBsAg • HBsAb • HBcAb • HCVAb • HCV RNA • HIV	• Human chorionic gonadotropin (WOCBP only) • FSH (women of nonchildbearing potential only)

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

8.5.3.1. Pregnancy Testing

At screening, post-menopausal women of nonchildbearing potential will have an FSH assessment (see Appendix A). Women of childbearing potential will have serum and urine pregnancy testing performed throughout the study as outlined in the SoA (see Table 3), as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

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

8.5.3.2. Serology

Hepatitis B and C and HIV screening assessments will be performed at the screening visit to rule out infection; required analytes are shown in Table 7. Generally, hepatitis and 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.

Eligibility criteria for participants with a history of HCV infection should generally require participants to have completed curative antiviral treatment and require HCV viral quantitative RNA below the limit of quantification 12 weeks after the end of HCV therapy. A participant who is HCVAb-positive but HCV RNA-negative due to prior treatment or natural resolution is eligible.

Reactivation of HBV can occur in chronic carriers of HBV infection (HBsAg-positive, undetectable or low HBV DNA, and normal ALT) who are not on HBV therapy or in individuals who have serologic evidence of a resolved prior HBV infection (ie, HBsAg-negative and anti-HBc–positive). While HBsAg-negative, anti-HBc–positive participants are at lower risk of HBV reactivation compared with HBsAg-positive participants, risk of HBV reactivation should be considered in all participants. Participants with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against HBV surface antigen as the only evidence of prior exposure may participate in the study.

8.6. Pharmacokinetic Assessments

Pharmacokinetic parameters will not be evaluated in this study.

8.7. Pharmacodynamic and Translational Assessments

Pharmacodynamic parameters are not evaluated in this study.

8.8. Unscheduled Visits

Unscheduled study visits may occur at any time at the investigator's (or designee's) discretion and appropriate clinical and laboratory tests may be performed as clinically indicated. Any assessments performed at those visits should be recorded in the eCRF.

8.9. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug, whether the participant is terminating the study early or the participant has completed the study, the EOT visit (at Week 4 EOT1 for end of DB VC period and at Week 8 EOT2 for end of OL period) should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. If a participant withdraws from the study before or on Week 4, EOT1 should be conducted. If a participant withdraws from the study after Week 4 and before or on Week 8, EOT2 should be conducted. The participant should be encouraged to complete the follow-up visit.

8.10. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 (+ 3) days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Reasonable efforts should be made to have the participant complete the follow-up visit and report any AEs that may occur during this period. Adverse events and SAEs must be reported up until at least 30 days after the last application of study drug or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant complete for the follow-up visit and report any AEs that may occur during this period.

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

9.1. Definition of Adverse Event

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

9.2. Definition of Serious Adverse Event

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

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

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History eCRF. For detailed information refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the 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 drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

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

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 30 days after the last application of study drug. If the investigator learns of any SAE, including death, at any time during this period, and he/she considers the event to be reasonably related to the study drug 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 drug under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its

designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

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

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

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

Serious Adverse Event Reporting

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

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. If a participant's treatment assignment is unblinded, the sponsor or its designee should be notified immediately by telephone for awareness.

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

9.7. Pregnancy

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

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

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

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

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

9.8. Warnings and Precautions

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

9.9. Product Complaints

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

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

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

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

9.10. Treatment of Overdose

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

10. STATISTICS

10.1. Sample Size Determination

Approximately 75 participants will be randomized 2:1 to ruxolitinib cream 1.5% BID or vehicle BID. The sample size calculation is based on the Fisher exact test for the primary efficacy endpoint. Based on the results from the 2 pivotal studies, INCB 18424-303 and -304, the response rate of EASI75 at Week 4 on head and neck is assumed to be 55% for the active arm of 1.5% BID versus 15% for placebo. Using a 2-sided alpha of 0.05, the sample size will have a > 90% power to detect a difference between the active treatment group versus vehicle. In addition, to provide adequate power for efficacy variables, the sample size is determined to provide a large database for safety evaluation.

10.2. Populations for Analysis

The populations for analysis are provided in Table 8.

Table 8: Populations for Analysis

Population	Description
FAS	The FAS includes all participants enrolled in the study who will have at least 1 application of study drug. The FAS will be used for the summary of demographics, baseline characteristics, participants disposition, and analyses of all efficacy and safety data.
OL-evaluable	The OL-evaluable population includes all participants who applied at least 1 dose of ruxolitinib cream during the OL period. All analyses for the OL period will be conducted with the OL-evaluable population.

10.3. Level of Significance

A hypothesis test will be conducted for the primary analysis at the 2-sided alpha = 0.05 level. In addition, 95% CI will be reported, if applicable.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary endpoint of this study is the proportion of participants who achieve an EASI75 of the head and neck region at Week 4. The primary analysis will be based on the FAS population. The primary alternative hypothesis (superiority of ruxolitinib 1.5% BID compared with vehicle) will be tested using a CMH test stratified by the stratification factor (screening face and/or neck IGA score). Odds ratio in response rates (ruxolitinib cream vs vehicle) at Week 4 will also be computed, and p-values will be provided. The difference in proportion of participants who achieve an EASI75 score of the head and neck region (ruxolitinib cream vs vehicle) at Week 4 will also be computed.

All nonresponders in the DB treatment period, as well as all participants who discontinue study treatment at any time before the timepoint of interest, or withdraw from the study for any reason, will be defined as nonresponders for the nonresponder imputation analysis.

10.4.2. Secondary [redacted] Analyses

All secondary [redacted] efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Continuous efficacy endpoints, including the actual measurement, change from baseline, and percentage change from baseline may also be analyzed by the mixed-effect model with repeat measurement.

10.4.3. Safety Analyses

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

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

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

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study 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.

11.2. 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, 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.

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 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 his/her 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. The study site will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - 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 woman of childbearing potential 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, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea 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 child-bearing 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. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	28 JUL 2021
Amendment 2:	04 AUG 2022

Amendment 2 (04 AUG 2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to align the protocol design with the DCT study delivery model. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities; Figure 1: Study Design Schema); Section 4.2, Overall Study Duration; Section 5.4, Screen Failures; Section 8.1.1, Informed Consent Process; Section 8.1.2, Screening Procedures; Section 8.5.3, Laboratory Assessments**

   Description of change: Updated screening window 35 days (5 weeks).

   Rationale for change: To accommodate the screening activities in the DCT model, especially to allow time for study drug delivery to participants' home.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities; Figure 1: Study Design Schema); Section 4.2, Overall Study Duration; Section 6.6, Concomitant Medications and Procedures; Section 8.5.1, Adverse Events; Section 8.10, Safety Follow-Up; Section 9.4, Reporting of Serious Adverse Events**

   Description of change: Updated safety follow-up and follow-up after the last application of study drug to 30 days.

   Rationale for change: To be consistent with safety reporting requirements.

3. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Inclusion Criteria 5 and 6); Section 6.1, Study Treatments Administered**

   Description of change: Clarified when randomization occurs.

   Rationale for change: In the DCT model, a participant is randomized during the screening period, not at baseline, after eligibility is confirmed from the screening visit.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 7.2, Participant Withdrawal From the Study; Section 8.1.2, Screening Procedures; Section 8.2, Efficacy Assessments**

   Description of change: Revised IGA and BSA assessments to be performed during baseline prior to dose administration.

   Rationale for change: Assessments perform at baseline will be used to confirm participant eligibility to continue with the study. Participants with disease activity outside of the protocol-defined range at the baseline visit will be early terminated and withdrawn from the study, and not deemed as a screen failure.

5. **Section 1, Protocol Summary; Section 5.4, Screen Failures; Section 6.2, Preparation, Handling, and Accountability; Section 7.3, Lost to Follow-Up; Section 8.1.2, Screening Procedures; Section 8.1.4, Distribution of Reminder Notification and eDiary**

   Description of change: Minor revisions and clarifications made to text.

   Rationale for change: To align with DCT model.

[redacted]

7. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added that study drug will also be collected during Week 4 at the end of the DB VC period.

   Rationale for change: The study drug collection during Week 4 was inadvertently excluded from the table.

8. **Section 2.2, Study Rationale**

   Description of change: Updated to include the details of the approval of ruxolitinib 1.5% cream.

   Rationale for change: To provide most up to date information.

9. **Section 2.2.1, Scientific Rationale for Study Design; Section 8.2, Efficacy Assessments**

   Description of change: Revised to include a rater in addition to an investigator for efficacy assessments.

   Rationale for change: To clarify that clinical assessments are assessed independently by rater(s) and not the investigator(s).

10. **Section 5.2, Exclusion Criteria (Exclusion Criterion 4b)**

    Description of change: Updated washout to 4 weeks.

    Rationale for change: To be consistent with other ruxolitinib cream study protocol(s) considering the short half-life of these immunomodulating agents.

11. **Section 5.2, Exclusion Criteria (Exclusion Criterion 7c)**

    Description of change: Revised criteria to clarify the exception for the ULN of total bilirubin applies to participants with Gilbert's Syndrome.

    Rationale for change: To clarify the relationship between the total versus direct bilirubin criteria.

12. **Section 5.2, Exclusion Criteria (Exclusion Criterion 8); Section 8.5.3, Laboratory Assessments (Table 7: Required Laboratory Analytes); Section 8.5.3.2, Serology**

    Description of change: Revised HBV and HCV criteria for participants who are positive for HCVAb, which requires additional laboratory assessments of HCV RNA. Updated language to be consistent with the laboratory testing procedures and clarified requirements for test results.

    Rationale for change: Due to DCT model, all required HBV and HCV tests are to be performed at the same time (ie, no reflective tests).

13. **Section 5.3, Lifestyle Consideration**

    Description of change: Updated to address participant's living environment and schedule.

    Rationale for change: Study will be conducted through televisits and mobile nurse home visits. Suitable living environments (eg, internet connect) are important for study conduct.

14. **Section 5.4, Screen Failures**

    Description of change: Added that participants that were terminated before dose administration could be rescreened upon sponsor approval.

    Rationale for change: Due to DCT model, the baseline visit is separate from randomization. A participant may be terminated from the study after randomization but before baseline visit/dose administration due to various reasons. Upon sponsor approval, a participant can be rescreened.

15. **Section 6.1, Study Treatments Administered; Section 6.5.2, Criteria for Permanent Discontinuation of Study Drug; Section 7.1.1, Reasons for Discontinuation**

    Description of change: Updated follow-up action to discontinue study treatment when total BSA to be treated exceeds 20%.

    Rationale for change: To be consistent with other ruxolitinib cream AD protocols.

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

    Description of change: Clarified that stratified by screening face and/or neck IGA score

    Rationale for change: In the DCT model for this study, only screening IGA is available at randomization. Participants are stratified based on screening IGA score.

17. **Section 10.2, Population for Analysis (Table 8: Population Analysis); Section 10.4.1, Primary Analysis**

    Description of change: The FAS population replaced both the ITT and safety populations.

    Rationale for change: For the DCT model for this study, randomization occurs in the screening period and not on Day 1/baseline; therefore, using ITT may include randomized but participants who are terminated from the study early (eg, due to not meeting disease activity criteria at baseline or other reasons) without any baseline values for analysis. Therefore, change from baseline analysis with ITT may not be feasible. The FAS will allow for a meaningful definition of change from baseline in the endpoints.

18. **Section 10.4.1, Primary Analysis**

    Description of change: Change primary analysis from logistic regression to CMH analysis.

    Rationale for change: To better characterize the effect size of the efficacy endpoints.

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

Amendment 1 (28 JUL 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise Exclusion Criterion 7 to create consistency across other atopic dermatitis protocols and for ease of recruitment, minimizing screen failures for nonsignificant clinical laboratory results. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Treatment Groups and Duration); Section 6.3, Measures to Minimize Bias: Randomization and Blinding**

   Description of change: The words "and age" were removed from the description of randomization and stratification of participants.

   Rationale for change: This study will only stratify by face and/or neck IGA score (2 vs 3).

2. **Section 5.2, Exclusion Criteria (Exclusion Criterion 2f)**

   Description of change: Added "day" to 880 µg (880 µg/day).

   Rationale for change: Clarification.

3. **Section 5.2, Exclusion Criteria (Exclusion Criterion 4e)**

   Description of change: Added a topical antipruritic and PDE4 inhibitors to the 1-week washout period before baseline.

   Rationale for change: In order to mitigate any risk to the participant and interference with interpretation of study data.

4. **Section 5.2, Exclusion Criteria (Exclusion Criteria 7 and 11)**

   Description of change: Clarified that Exclusion Criterion 7 applies to laboratory results at screening; deleted Exclusion Criteria 7a (any value < 0.75 × LLN [other than bilirubin]) and 7b (any value > 2.5 × ULN); clarified that Exclusion Criterion 7c applies to liver function tests and added AST or ALT ≥ 2.5 × ULN; moved Exclusion Criterion 11 to 7d; and added Exclusion Criteria 7e, 7f, and 7g regarding cytopenias at screening, estimated glomerular filtration rate, and any other clinical significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant, respectively.

   Rationale for change: Original Exclusion Criterion 7a was overly restrictive; Criteria 7c through 7g were added/moved to be consistent with exclusion criteria from other atopic dermatitis protocols. Exclusion Criterion 11 was moved because it is an investigator-determined clinically significant abnormal value.

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

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