Official Title: An Open-Label, Single-Ar**m**, Phase 4 Study **o**f **R**uxolitinib Cream in Adults with Ato**p**ic Dermatitis Experiencing Sleep Disturbance in t**he** **U**nited **S**tates (Morpheus)

NCT Number: NCT05696392

Document Date: Protocol INCB 18424-902 Version 1 21 JUNE 2022

Clinical Study Protocol

INCB 18424-902

An Open-Label, Single-Arm, Phase 4 Study of Ruxolitinib Cream in Adults with Atopic Dermatitis Experiencing Sleep Disturbance in the United States (Morpheus)

Product:	**Ruxolitinib Cream**
IND Number:	[redacted]
Phase of Study:	**4**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**21 JUNE 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-902 Protocol (dated 21 JUNE 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AD	atopic dermatitis
AE	adverse event
AI	artificial intelligence
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration (US)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GPS	global positioning satellite
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment

Abbreviations and Special Terms	Definition
IRB	institutional review board
IRT	interactive response technology
JAK	Janus kinase
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numerical rating scale
PDE-4	phosphodiesterase-4
PP	per protocol
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PSG	polysomnography
REM	rapid eye movement
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORAD	scoring atopic dermatitis
SE	sleep efficiency
SoA	schedule of activities
SOL	sleep onset latency
SOP	standard operating procedure
SPF	sun protection factor
STOP-BANG	snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, and gender
STP	sufficiently treated population
TEAE	treatment-emergent adverse event
TST	total sleep time
ULN	upper limit of normal
WASO	wake after sleep onset
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

An Open-Label, Single-Ar**m**, Phase 4 Study **o**f **R**uxolitinib Cream in Adults with Ato**p**ic Dermatitis Experiencing Sleep Disturbance in t**he** **U**nited **S**tates (Morpheus)

Protocol Number: INCB 18424-902

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the reduction in sleep disturbance after using ruxolitinib cream	Change from baseline in TST as measured by Ōura Ring wearable device at Week 8
Secondary	
To further evaluate the reduction in sleep disturbance after using ruxolitinib cream	Change from baseline in PROMIS Sleep Disturbance – Short Form 8b score (24-hour recall) at Week 8

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 4
Clinical Indication	Atopic dermatitis
Population	Male and female adults (≥ 18 years of age) with a diagnosis of AD for at least 2 years, BSA involvement of 3% to 20% (excluding scalp), an IGA score ≥ 2, Itch NRS ≥ 4, PROMIS Sleep Disturbance – Short Form 8b score ≥ 21, average Total Sleep Time/night ≤ 6.5 hours, and no underlying sleep disorders
Number of Participants	Approximately 100 participants will be enrolled. The study will be conducted at approximately 30 sites in the US.
Study Design	Open-label, single-arm, Phase 4 study of ruxolitinib cream in patients with AD who experience sleep disturbance.
Estimated Duration of Study Participation	Participants will participate for a total of up to 128 days as follows: • Up to 42 days in the screening period (includes a 7-day screening sleep assessments used in determining eligibility and a 7-day pretreatment sleep assessment to further determine eligibility and to establish the participant's baseline sleep pattern) • 56 days in the treatment period • 30 days in the safety follow-up period.
DSMB/DMC	No
Coordinating Principal Investigators	April Armstrong, MD, MPH Eric Simpson, MD, MCR

Treatment Groups and Duration:

This is a Phase 4, multicenter, open-label, single-arm study to evaluate the reduction in sleep disturbance among participants with AD after treatment with ruxolitinib cream. This study will enroll approximately 100 adults (≥ 18 years of age) with at least mild severity AD who have sleep disturbance. Individuals with known sleep-related conditions that are not associated with their AD diagnosis will be excluded from the study.

A minimally invasive wearable device (Ōura Ring) and a [redacted] will be used to collect objective measures of sleep during the study. The Ōura Ring will be used during a 7-day screening sleep assessment (to determine study eligibility), and both technologies will be used during a 7-day pretreatment sleep assessment (to further determine eligibility and to establish baseline sleep patterns) as well as throughout the 8-week treatment period (to monitor postbaseline sleep patterns).

All participants will apply ruxolitinib cream at the FDA-approved strength (1.5%) BID over the 8-week treatment period, during which participants will treat all baseline AD lesions BID, regardless of whether or not the lesion(s) improve. New and/or expanded areas of AD may also be treated but not in excess of a total of 20% BSA (for original plus new areas) per application.

All participants will have follow-up assessments 30 (+ 7) days after the end of treatment (Week 8/EOT or ET) to evaluate safety.

Table 3: Schedule of Activities

Visit Day (Range)/ Visit Week	Screening Period[a]		Treatment Period			Safety Follow-Up Period	Notes
	Days -42 to -7	Days -7 to -1	Day 1/ Baseline	Week 4 (± 7 days)	Week 8 (+ 7 days)/ EOT/ET	30 (+ 7) Days after Last Application	
Administrative Procedures							
Informed consent	X						Section 8.1.1
Inclusion/exclusion criteria	X		X*				*Reassess applicable inclusion/exclusion criteria; Section 5
Demography and general medical history	X						Section 8.1.5.1
Relevant medical and treatment history	X						Section 8.1.5.2
Prior/concomitant medications	X		X	X	X	X	Section 6.6
Contact IRT	X		X	X	X		Section 8.1.3
Ōura Ring wearable device set-up	X						
[redacted]							
eDiary set-up	X						Set-up includes giving participants access to the eDiary; Section 8.1.4
Application of study drug BID			X	X	X		First application occurs on Day 1 at the site under direct site staff supervision; subsequent applications are at home; applications are recorded in the eDiary; Section 6.1
Review the participant's eDiary			X	X	X		
Dispense study drug			X	X			
Collect study drug				X	X		
Study drug accountability				X	X		Section 6.4

Table 3: Schedule of Activities (Continued)

Visit Day (Range)/ Visit Week	Screening Period[a]		Treatment Period			Safety Follow-Up Period	Notes
	Days -42 to -7	Days -7 to -1	Day 1/ Baseline	Week 4 (± 7 days)	Week 8 (+ 7 days)/ EOT/ET	30 (+ 7) Days after Last Application	
Efficacy Assessments							
Ōura Ring wearable device data collection	X*	X	X	X	X		*Includes collection of TST data for 7 days (screening sleep assessment) to confirm eligibility; Section 8.2.1
[redacted]							
IGA	X		X	X	X		Section 8.2.3
Total %BSA	X		X	X	X		Section 8.2.4
Photographs of target lesion			X	X	X*		Photographs taken on-site on Day 1 and then at home weekly through Week 8. *The Week 8 photographs may be taken at home or at the site during the visit; Section 8.2.5
Patient Reported Outcomes							
STOP-BANG	X						Only complete the 4 questions from STOP portion of questionnaire; Section 8.3.1
[redacted]							
PROMIS Sleep-Related Impairment – Short Form 8b	X	X*	X*	X*	X*		Completed via eDiary (in the morning); Section 8.3.3 *Completed daily from pretreatment sleep assessment through last application of study drug.
[redacted]							

Table 3: Schedule of Activities (Continued)

Visit Day (Range)/ Visit Week	Screening Period[a]		Treatment Period			Safety Follow-Up Period	Notes
	Days -42 to -7	Days -7 to -1	Day 1/ Baseline	Week 4 (± 7 days)	Week 8 (+ 7 days)/ EOT/ET	30 (+ 7) Days after Last Application	
Safety assessments							
AE assessments	X	X	X	X	X	X	Section 8.4.1
Comprehensive physical examination	X						Section 8.4.2
Targeted physical examination			X	X	X	X	Conducted only when indicated by symptoms reported by participant (AEs or other findings); Section 8.4.2
Vital signs	X*		X	X	X	X†	* Height and weight at screening only. †If this is a telehealth visit, vital signs are not collected; Section 8.4.3

[a] The screening period includes two 7-day sleep assessments: the screening sleep assessment (Days −42 to −7) and the pretreatment sleep assessment (Days −7 to −1).

Table 4: Schedule of Laboratory Assessments

Visit Day (Range)/ Visit Week	Screening Period[a]		Treatment Period			Safety Follow-Up Period	Notes
	Days −42 to −7	Days −7 to −1	Day 1/ Baseline	Week 4 (± 7 days)	Week 8 (+ 7 days)/ EOT/ET	30 (+ 7) Days after Last Application	
Laboratory Assessments							
Serum chemistries	X				X	X	Section 8.4.4
Hematology	X				X	X	Section 8.4.4
HIV	X						Section 8.4.4.2
Pregnancy testing (WOCBP only)	X		X	X	X	X	Serum test at screening. Urine test at all other specified visits. A positive urine test must be confirmed by a serum test. Section 8.4.4.1
FSH	X						For female participants of nonchildbearing potential. Section 8.4.4

[a] The screening period includes two 7-day sleep assessments: the screening sleep assessment (Days −42 to −7) and the pretreatment sleep assessment (Days −7 to −1).

2. INTRODUCTION

2.1. Background

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate, an investigational product that has been developed for the treatment of inflammatory diseases of the skin. Ruxolitinib phosphate is an inhibitor of the JAK family of protein tyrosine kinases, which play important roles in signal transduction downstream of cytokine and growth factor receptors. Ruxolitinib has shown efficacy in various chronic inflammatory conditions that present with an aberrant production of cytokines and growth factors, including psoriasis, vitiligo, and AD. In the US, Opzelura™ (ruxolitinib) cream is FDA-approved for the topical short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (Opzelura 2021).

2.1.1. Atopic Dermatitis and Itch

Atopic dermatitis is a chronic, recurring, and highly pruritic inflammatory skin condition characterized by erythematous lesions, xerosis, and frequent skin infections (Al-Shobaili et al 2016, Ong et al 2002). It typically begins early in infancy or childhood, although it can also develop in adulthood, and is more frequent among females than males (1.3 to 1.0 ratio; Eichenfield et al 2014, Leung et al 2012). Several environmental factors, such as small family size and increased education, can heighten one's likelihood to develop AD; however, recent advancement in the molecular genetics of the disease indicate that AD may result from the inheritance of disease susceptibility variants of genes coding for constituents of the skin barrier and immune system (Al-Shobaili et al 2016, Leung et al 2012). Evidence suggests that a complex interplay between these genes and environmental factors results in defective skin barrier integrity and altered immunologic/inflammatory responses and contributes to the development, progression, and chronicity of AD (Al-Shobaili et al 2016, Leung et al 2012, National Eczema Association 2018, Rerknimitr et al 2017).

One of the most prominent and debilitating symptoms of AD is pruritus, also referred to as an "unpleasant sensation eliciting the urge to scratch" (Darsow et al 2011, Leung et al 2012, Rerknimitr et al 2017, Yarbrough et al 2013). In most cases, this urge to scratch arises following exposure to triggering factors, such as irritants, allergens, infectious agents, and/or emotional stressors, which elicit a cutaneous hyper-reaction (Darsow et al 2011). The mechanical injury from scratching contributes to skin inflammation and exacerbates the scratch-itch cycle that perpetuates the disease (Leung et al 2012). Pruritus affects the majority of patients with AD, and can be significantly bothersome and undermine the affected patient's quality of life and overall well-being (Farmer and Marathe 2017, Mochizuki et al 2017, Yosipovitch and Papoiu 2008). It can also disturb sleep and cause psychological problems such as depression and anxiety (Yarbrough et al 2013). Given the central role of pruritus in AD, it has become clear that the control of itch is critical to the management of the disease (Pavlis and Yosipovitch 2018, Yarbrough et al 2013).

Free nerve endings in the skin are involved in pruritus as itching receptors (Urashima and Mihara 1998). Histological examinations have revealed increased cutaneous

nerve densities in patients with AD and animal models, suggesting that this higher density may be at least partly responsible for intense itching in the skin. The increased nerve fibers in the epidermis may be also activated by exogenous mechanical, chemical, and biological stimuli, resulting in itch responses. Previous observations suggest that an increase in nerve density in the epidermis may be caused by weakness or disruption of skin barrier function, allowing the invasion of exogenous substances into the skin. As itch is a biological sign, it is important for antipruritic therapy in AD to target cutaneous nerve fibers, their triggers, and barrier function (Tominaga and Takamori 2014).

Efforts have been made to find new and more appropriate treatment options to better meet the current and future medical needs of patients with AD. The results of recent trials indicated that oral JAK inhibitors may be effective in the treatment of AD and have elicited interest in the use of this drug class as a topical treatment for AD (Bissonnette et al 2019, Guttman-Yassky et al 2019, Levy et al 2015). Recent studies suggest that JAK inhibition may have antipruritic effects by acting directly on sensory nerve fibers (Hashimoto et al 2019). Ruxolitinib cream offers a novel therapeutic approach in AD with dual anti-inflammatory and antipruritic properties, providing a rationale for investigating the clinical utility of ruxolitinib cream for the treatment of this condition. Additionally, given that pruritus associated with AD causes significant patient discomfort, often leading to sleep deprivation or poor sleep quality, treatment of AD with ruxolitinib cream may positively impact patients' sleep-related qualify of life.

2.2. Study Rationale

Atopic dermatitis is the most common inflammatory skin disease that is chronically relapsing and characterized by associated pruritis (Leung and Guttman-Yassky 2014). Sleep disturbance is associated with AD and is a major contributing factor in reduced quality of life (Ricci et al 2007). In addition to the individuals with AD, family members also reported that sleep disturbance is one of the greatest factors affecting their quality of life (Ricci et al 2007). Sleep disturbance is reported in up to 83% of children with AD and up to 87% of adults with AD (Camfferman et al 2010, Chang and Chiang 2018).

Data from previous studies demonstrated that topical ruxolitinib cream is effective in treating AD due to its dual anti-inflammatory and antipruritic properties. In addition to demonstrating a higher proportion of study participants with AD achieving clear or almost clear status (Papp et al 2021), participants also reported significant reduction in sleep disturbance through PROMIS® and SCORAD PROs compared to vehicle control group (Simpson et al 2021).

The goal of the study is to demonstrate the reduction in sleep disturbance among participants with AD after the application of ruxolitinib cream using wearable and wireless technologies that enable objective measures of sleep.

2.2.1. Scientific Rationale for Study Design

In the 2 completed Phase 3 adult and adolescent AD trials of ruxolitinib cream versus vehicle control (INCB 18424-303 and INCB 18424-304), the ruxolitinib 1.5% cream group in each study demonstrated reduction in sleep disturbance based on PROs (PROMIS sleep disturbance questionnaire and SCORAD) at Week 8 (Papp et al 2021, Simpson et al 2021). In INCB 18424 -303, more participants reported clinically meaningful improvement in the PROMIS sleep disturbance questionnaire score (≥ 6-point improvement from baseline) at

Week 8 with ruxolitinib 1.5% cream versus vehicle ($p < 0.01$), and in INCB 18424-304, response rates were also higher with ruxolitinib 1.5% cream versus vehicle, although the differences were not statistically significant.

Although PROMIS is a validated PRO measure of sleep, it has the limitation of subjectivity; while some subjective measures of sleep may correlate with sleep patterns of individuals, objective measures of sleep may provide a more robust assessment of the effect of ruxolitinib cream on sleep disturbance among patients with AD (O'Donnell et al 2009). Only a small number of studies in AD have been conducted using objective measures of sleep-related metrics (Chang and Chiang 2018, Chang et al 2014) while the majority of the studies rely on PROs.

Polysomnography is traditionally used as the gold standard for determining sleep disturbance and other sleep-related conditions, and it is the standard to objectively measure sleep in clinical settings (Boe et al 2019, Shrivastava et al 2014). Polysomnography is usually conducted in a sleep laboratory and requires the participant to be connected to dozens of electrodes. However, due to the complexity of the usage and physical size of the machinery involved, the use of PSG devices would not be practical in an 8-week ambulatory study.

In recent years, alternative technologies (eg, wearable and wireless devices) have been developed to assess sleep metrics using combinations of actigraphy and biometric data and have been shown to produce data comparable to PSG (Chee et al 2021, Kinnunen 2016). Such recent developments in wearable and wireless technologies allow for the measurement of sleep-related parameters without requiring polysomnographic machines (Boe et al 2019). This study will use a minimally invasive wearable device (Ōura Ring) [redacted] for collecting objective measures of sleep during the study. Ōura Ring is a commercially available device that participants will wear on their fingers and that can be used for monitoring sleep status

[redacted]

The eligible study population will be similar to that in the ruxolitinib cream Phase 3 studies (INCB 18424-303 and INCB 18424-304; eg, BSA 3-20%); however, baseline Itch NRS ≥ 4 and PROMIS Sleep Disturbance – Short Form 8b score ≥ 21 are 2 key differences that have been included in this study. Also due to the high variability in sleep patterns among adolescents (Carskadon 1982), this study will be limited to adults (age ≥ 18 years). To establish eligibility, the sleep disturbance of participants will be assessed using the wearable device during the screening period. These additional measures are intended to more robustly evaluate participants who have at least moderate itch from AD and at least moderate sleep disturbance, so that the effect of ruxolitinib 1.5% cream on these particularly burdensome aspects of the disease can be better quantified (Eckert et al 2017).

The sleep patterns of individuals are documented to be highly variable (Vallières et al 2005). Therefore, this study is designed to have each participant serving as their own control with a pretreatment sleep assessment prior to initiating the treatment with ruxolitinib cream.

2.2.2. Justification for Dose

The results of the completed ruxolitinib cream Phase 3 AD trials (INCB 18424-303 and INCB 18424-304) demonstrated ruxolitinib 1.5% cream is a safe, well-tolerated, and effective treatment for participants with mild to moderate AD. All participants in this study will apply ruxolitinib cream with the FDA-approved strength (1.5%) and application frequency (BID) (Opzelura 2021), using the same treatment paradigm as in the Phase 3 AD trials. New and/or expanded areas of AD may also be treated but not in excess of a total of 20% BSA (for original plus new areas) per application.

2.3. Benefit/Risk Assessment

Ruxolitinib cream showed statistically significant and clinically meaningful improvement in AD. Given that participants in this study will have a diagnosis of active AD, it is likely that these participants will benefit from ruxolitinib cream treatment. Additionally, given that, participants in this study will also be experiencing sleep disturbance, which may be a result, in part, of the discomfort associated with AD, it is possible that these participants will have a benefit to their sleep following treatment of their AD with ruxolitinib cream.

Safety data from the Phase 3 AD studies (INCB 18424-303 and INCB 18424-304) demonstrate that ruxolitinib 1.5% cream BID applied continuously for 8 weeks followed by prolonged (44 weeks) intermittent use was safe and well-tolerated. The TEAEs were generally Grade 1 or 2 in severity and were most often events of nasopharyngitis and upper respiratory tract infection. Frequencies of these events were within the expected range for the general AD population.

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

A comprehensive analysis of potential systemic safety concerns with oral ruxolitinib as well as additional events of interest for oral JAK inhibitors that have not been observed with oral ruxolitinib was performed in the Phase 3 studies. Events of interest included cytopenias, herpes zoster and other viral skin infections, other infections and infestations, nonmelanoma skin neoplasms, liver function test and lipid elevations, and arterial and venous thromboembolic and thrombocytosis events. As expected given the low bioavailability and the low plasma concentrations of ruxolitinib observed following topical application, ruxolitinib 1.5% cream BID was not associated with these safety concerns.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ruxolitinib cream may be found in the IB and the prescribing information for Opzelura (Opzelura 2021).

In addition, to address challenges associated with the COVID-19 global pandemic, the sponsor has issued Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain (see Appendix B).

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the reduction in sleep disturbance after using ruxolitinib cream	Change from baseline in TST as measured by Ōura Ring wearable device at Week 8
Secondary	
To further evaluate the reduction in sleep disturbance after using ruxolitinib cream	Change from baseline in PROMIS Sleep Disturbance – Short Form 8b score (24-hour recall) at Week 8
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4, multicenter, open-label, single-arm study to evaluate the reduction in sleep disturbance among participants with AD after treatment with ruxolitinib 1.5% cream. This study will enroll approximately 100 adults (≥ 18 years of age) with at least mild severity AD who have sleep disturbance. Individuals with known sleep-related conditions that are not associated with their AD diagnosis will be excluded from the study. The study will be conducted at approximately 30 sites in the US.

A minimally invasive wearable device (Ōura Ring) and a [redacted] will be used to collect objective measures of sleep during the study. The Ōura Ring will be used during a 7-day screening sleep assessment (to determine study eligibility), and both technologies will be used during a 7-day pretreatment sleep assessment (to further determine eligibility and to establish baseline sleep patterns) as well as throughout the 8-week treatment period (to monitor postbaseline sleep patterns).

Figure 1 presents the study design schema, and Table 3 presents the SoA.

The study begins with an up to 42-day screening period, which includes two 7-day sleep assessments (the screening sleep assessment and the pretreatment sleep assessment). During the screening period, participants will be given access to an electronic diary (eDiary) to complete PROs during the study, and participants will discontinue any current treatments for AD as well as other excluded treatments.

Following completion of the pretreatment sleep assessment, participants will continue into an 8-week treatment period. On Day 1 of the treatment period, all eligible participants will be enrolled in the study and will begin treating their AD with ruxolitinib cream at the FDA-approved strength (1.5%) BID, applied topically as a thin film. All original areas of AD involvement identified on Day 1 (baseline), regardless of whether or not the lesion(s) improve, and any new and/or expanded areas of AD lesions will be treated until the morning of the Week 8 visit, with a total maximum allowed treatment area of ≤ 20% BSA. Sleep data from each participant will be continuously collected during the treatment period (Day 1 through Day 56 inclusive [or the day before the Week 8 visit]) with both sleep monitoring devices. Measurements of sleep at Week 8 will be compared to baseline in a pair-wise manner to determine the reduction in sleep disturbance. At the end of the treatment period (Week 8/EOT or ET), participants will discontinue treatment with ruxolitinib 1.5% cream (with the last application on the morning of this visit) and will be required to return the eDiary, Ōura Ring, and [redacted]

Following completion of the treatment period (or the last application of study drug for those who discontinue early), participants will have follow-up assessments 30 (+ 7) days after the end of treatment to evaluate safety.

Throughout the study, at the times indicated in the SoA (see Table 3), participants will complete the following PROs using their eDiary: Itch NRS (daily), PROMIS Sleep Disturbance – Short Form 8b (daily), and PROMIS Sleep-Related Impairment – Short Form 8a (weekly). Additionally, the STOP portion of the STOP-BANG questionnaire will be completed during the screening visit as part of the eligibility assessment. Participants will be assessed for the safety

and tolerability of ruxolitinib cream throughout the study by monitoring the type, frequency, and severity of AEs, performing physical examinations, measuring vital signs, and conducting clinical laboratory assessments, as outlined in the SoA.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study.

It is estimated that an individual will participate for up to approximately 128 days (42-day screening period, 56-day treatment period, and 30-day safety follow-up period). A participant is considered to have completed the study if they have completed all study procedures of the study including the last visit or the last scheduled procedure shown in Table 3 as well as successfully submitted sleep data.

4.3. Study Termination

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

The sponsor may terminate the study electively, or if required by regulatory agency. In the event of significant safety findings, the study will be terminated. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for this study.

   Note: Consent must be obtained prior to any study-related procedures.
2. Male or female participant ≥ 18 years of age at screening.
3. Has clinically confirmed diagnosis of active AD according to Hanifin and Rajka (1980) criteria.
4. Has at least a 2-year history of AD (information obtained from medical chart, participant's physician, or directly from the participant).
5. Has chronic pruritus related to AD for at least 3 months before the screening visit (information obtained from medical chart, participant's physician, or directly from the participant).
6. Has an overall BSA affected by AD of 3%-20% (excluding scalp) at the screening and baseline visits.
7. Has an IGA score ≥ 2 at the screening and baseline visits.
8. Has an Itch NRS score ≥ 4 at the screening and baseline visits.
9. Willing to complete the once-daily Itch NRS (24-hour recall period) entries at approximately the same time each day during the study.
10. Has a PROMIS Sleep Disturbance – Short Form 8b score ≥ 21 at the screening visit.
11. Has an average TST/night of ≤ 6.5 hours during the 7-day screening sleep assessment, as measured by Ōura Ring wearable device.
12. Has habitual amount of time in bed attempting to sleep of at least 7 hours, as reported by the participant.
13. Has access to broadband wireless internet and is willing to connect wireless device to the wireless network.
14. Agrees to spend at least 95% of nights in the household during the study period.
15. Has habitual bedtime time that falls between 9:00 pm and 12:00 am (midnight) and habitual wake time that falls between 5:00 am and 9:00 am.
16. Agrees to maintain a regular sleep schedule during the study period.

17. Generally does not experience sleep disturbance due to factors such as having young children (< 5 years) who live in the household or pets.
18. Willing and able to follow required study procedures for measuring sleep for the duration of the study.
19. Willing to avoid pregnancy or fathering children based on the below criteria:
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of study 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 and a negative urine pregnancy test before the first application at baseline/Day 1 and must agree to take appropriate precautions to avoid pregnancy from baseline through 30 days (1 menstrual cycle) after the last application 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.
20. Willing to comply with all study procedures and restrictions including discontinuation of all current therapies for AD and pruritus (unless otherwise specified), and must be available for the duration of the study.
21. Willing to adhere to limited alcohol and caffeine use in a way that it does not impact general sleep pattern and willing to record alcohol and caffeine use for the duration of the study.

5.2. Exclusion Criteria

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

1. Participant is a female who is breastfeeding, pregnant, or planning to become pregnant during the study.
2. Currently using a wearable or other device for monitoring sleep patterns and unwilling to discontinue its use during the study.
3. Currently has a schedule that includes nighttime work shifts.
4. Has had significant flares or unstable course in AD (ie, condition worsened significantly or required significant change in medications, as per medical judgment) in the previous 4 weeks before screening (information obtained from medical chart, participant's physician, or directly from the participant).
5. Has a clearly defined etiology for pruritus other than AD, including but not limited to urticaria, psoriasis, or other nonatopic dermatologic conditions; hepatic or renal disease; psychogenic pruritus; drug reaction; uncontrolled hyperthyroidism; and infection.

6. Any current and/or history of serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including application of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
    a. Clinically significant or uncontrolled cardiovascular disease unless approved by the medical monitor/sponsor:
        – Unstable angina
        – Acute myocardial infarction or stroke within 6 months from Day 1 of study cream application
        – New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mm Hg).
    b. Current and/or history of malignancy in the 5 years preceding the baseline visit, except for adequately treated, nonmetastatic nonmelanoma skin cancer.
    c. Current and/or history of arterial or venous thrombosis, including deep vein thrombosis and physical exam.
    d. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.
    e. Has a current or prior diagnosis of any sleep-related condition (eg, insomnia not solely related to AD, severe sleep apnea, restless leg syndrome, narcolepsy).
    f. History of drug or alcohol dependency or abuse within approximately the previous 1 year.
    g. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night.
    h. Participants answering yes to all 4 of the following STOP questions from the STOP-BANG questionnaire:
        – Do you snore loudly? (Louder than talking or loud enough to be heard through closed doors)
        – Do you often feel tired, fatigued, or sleepy during the daytime?
        – Has anyone observed you stop breathing during sleep?
        – Do you have (or are you being treated for) high blood pressure?
    i. Has clinically infected AD or has used antibiotics (systemic or topical) for their infected AD within 2 weeks prior to the screening period.
    j. Has immune deficiency or is immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
    k. Has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments (eg, generalized erythroderma, Netherton syndrome, psoriasis, or any skin condition other than AD that may risk inducing a pruritus flare/worsening).
    l. Has had a major surgery within 8 weeks prior to screening or has a major surgery planned during the study.
    m. Is on maintenance dialysis.
    n. Current or history of hepatitis B virus or hepatitis C virus infection.

7. Has any clinically significant laboratory/vital sign abnormality that would, in the opinion of the investigator, put the participant at undue risk or interfere with interpretation of study results.
8. Has any of the following clinical laboratory test results at screening:
   a. Hemoglobin < 100 g/L (ie, 10 g/dL) or ANC < 1000/µL
   b. Liver function tests:
      – AST or ALT ≥ 2.5 × ULN
      – Total bilirubin > 1.5 × ULN unless Gilbert syndrome
   c. Estimated GFR < 30 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation).
   d. Positive serology test results at screening for HIV antibody.
   e. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.
9. Use of any of the following treatments within the indicated washout duration prior to the pretreatment sleep assessment:
   a. 5 half-lives or 12 weeks, whichever is longer – marketed or investigational biologic agents (eg, dupilumab). For biologic agents with washout duration longer than 12 weeks (eg, rituximab), consult the medical monitor.
   b. 4 weeks – systemic (oral/injectable) treatments that could affect AD and/or pruritus, such as corticosteroids, adrenocorticotropic hormone analogs, cyclosporin, methotrexate, azathioprine, retinoids, calcineurin inhibitors, PDE-4 inhibitors, other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus), hydroxycarbamide [hydroxyurea], or opioids).
      Note: Intranasal and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
   c. 2 weeks – immunizations with live-attenuated vaccines; oral, sedative H_1 antihistamines (including but not limited to diphenhydramine and hydroxyzine).
      Note: Oral, nonsedative, H_1 antihistamines will be permitted during the study.
      Note: Live-attenuated vaccines are not recommended during the treatment period.
      Note: COVID-19 vaccination is allowed.
   d. 1 week – use of other topical treatments that could affect AD and/or pruritus (other than bland emollients; eg, Aveeno® creams, ointments, sprays, soap substitutes), such as topical antipruritics (eg, doxepin cream), corticosteroids, calcineurin inhibitors, PDE-4 inhibitors (eg, crisaborole), coal tar (shampoo), topical antibiotics, or antibacterial cleansing body wash/soap.
      Note: Diluted sodium hypochlorite "bleach" baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
10. Has received any ultraviolet B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to the screening period.
11. Has had psoralen plus ultraviolet A treatment within 4 weeks prior to the screening period.
12. Has received a nonbiological investigational product or device within 4 weeks prior to the screening period, or is currently enrolled in another investigational drug study.

13. Has received treatment with JAK inhibitors (systemic or topical) within 4 weeks prior to the screening period.
14. Has had prior treatment with a JAK inhibitor that was discontinued for safety reasons or tolerance problems.
15. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before baseline with a strong CYP3A4 inhibitor.
16. Has a known or suspected allergy to ruxolitinib or any component of the study drug.
17. Has a known history of clinically significant drug or alcohol abuse in the last year prior to screening.
18. Had night shift work hours in the past 3 months prior to screening.
19. Plans to work on an overnight shift during the study period.
20. Plans to travel more than 2 time zones during the study period.
21. Has other upcoming life events, or anticipates having life events, during the study period that would interrupt the participant's sleep at their household.
22. Has excessive caffeine use that, in the opinion of the investigator, contributes to the participant's insomnia or habitually consumes caffeine-containing beverages after 6:00 pm and is unwilling to forego caffeine after 6:00 pm for the duration of the study.
23. Has a 7-day average TST/night of > 7.5 hours during the pretreatment sleep assessment, as measured by Ōura Ring wearable device.
24. Is unlikely, in the opinion of the investigator, to be compliant with study procedures and requirements.

5.3. Lifestyle Considerations

Participants should be encouraged to sleep at home (or usual place of sleep) during the 14 days prior to Day 1, Week 4, and Week 8.

Participants should be encouraged to attempt to sleep for at least 7 hours of sleep each night during the study (excluding time watching television, reading, etc in bed).

[redacted]

Participants should be advised to limit alcohol intake to no more than 2 drinks per day or forego having alcohol within the 3 hours before bedtime for the duration of their participation in the study.

Participants should be advised to avoid drastically different sleep patterns over the weekend nights compared to weekday nights for the duration of the study.

Participants should be cautioned to avoid excessive exposure to natural or artificial sunlight (including tanning booths, sun lamps, etc).

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.

It is recommended that swimming should not take place within 2 hours before and after the planned study drug application.

Participants should be advised not to change medications taken for comorbid conditions unless deemed necessary by a healthcare professional.

Participants should be advised not to change, add or remove, medications and supplements that would change general sleep patterns unless deemed necessary by a healthcare professional.

5.4. Screen Failures

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

Laboratory tests with results that fail eligibility requirements may be repeated once during screening if deemed acceptable by the investigator. Additionally, participants who do not meet the criteria for participation in this study (screen failure) may be rescreened once, if deemed acceptable by the investigator. Participants who rescreen must reconsent (if rescreened > 42 days after the initial screening) and be assigned a new participant number.

Participants who do not meet the eligibility criteria for the Itch NRS score, PROMIS Sleep Disturbance – Short Form 8b score, or TST (during the screening sleep assessment or pretreatment sleep assessment, as measured by Ōura Ring) will be considered as screen failures and may not be rescreened.

5.5. Replacement of Participants

Participants meeting the following criteria may be replaced by enrolling additional participants:

- Participants who received less than 23 applications in any interval of 14 consecutive days of BID study drug administration.
- Participants with inadequate data (data missing for ≥ 3 days either during the pretreatment sleep assessment or between Days 49 and 56) to complete the primary analysis (eg, due to device malfunction, internet outage, unplanned travel, etc).
- Participants experiencing major changes to their sleep patterns due to a medical condition or other life situation.

6. STUDY TREATMENT

All participants enrolled in the study will be treated with open-label ruxolitinib 1.5% cream BID.

6.1. Study Treatment Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

Study treatment name:	Ruxolitinib
Mechanism of action:	JAK1 and JAK2 inhibitor
Dosage formulation:	Cream
Unit dose strength/ dosage level:	1.5%
Administration instructions:	Apply BID as a thin film to the affected area(s) (up to 20% BSA[a]), at an interval of approximately 12 hours (but at least 8 hours) for 8 weeks (from Day 1 until the morning of the Week 8visit).
Packaging and labeling:	Ruxolitinib will be provided in 60-g tubes. Tubes will include labeling in the local language, and each tube will be labeled as required per country requirement.
Storage:	Ambient (15°C-30°C/59°F-86°F)
Status of treatment in participating countries:	Approved in the US[b]

[a] Affected areas identified at baseline will be treated for 56 days and new and/or expanded areas of AD may be treated but not in excess of a total of 20% BSA (for original plus new areas) per application.
[b] Opzelura (ruxolitinib) cream

Ruxolitinib 1.5% cream will be supplied in 60-g tubes. The study drug will be provided by the sponsor and dispensed at the study visits summarized in the SoA (see Table 3).

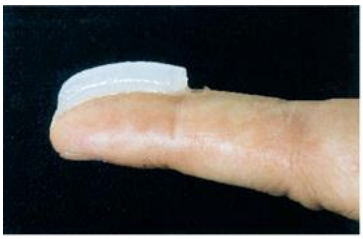
6.1.1. Study Treatment Application Guidance

On Day 1, study staff will instruct participants on proper application of study drug. Refer to the Study Pharmacy Manual for participant instructions for handling study of drug.

Study drug should be applied optimally at equal intervals (ie, approximately 12 hours apart, but at least 8 hours apart) to the affected areas in the morning and in the evening, with the evening application done at least 1 hour before bedtime if possible. Participants should continue to apply study drug throughout the 56-day treatment period to the affected areas identified on Day 1 (baseline) and any new AD lesions (up to a total maximum of 20% BSA for the original plus any new areas), regardless of whether the signs and symptoms of the participant's AD resolve during the treatment period. In the event that new lesions are outside of the original location(s) identified at baseline and/or are more widespread than at baseline, the participant is required to contact the site for approval to treat additional areas; this may occur via telephone, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit. The last planned application will be on the morning of the Week 8/EOT visit.

Participants should remove study drug from the tube with their fingertip in small amounts until all of the areas to be treated are covered by a thin even film. A fingertip unit (see Figure 2) allows for the thin spreading of the study drug to cover approximately 2% of the participant's total BSA.

Figure 2: Study Drug Application Using a Fingertip Unit



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

6.2. Preparation, Handling, and Accountability

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

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

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

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

The study drug must be used only in accordance with the Protocol. The investigator or designee 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 study drug 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 destruction according to institutional SOPs. If; however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the study drug supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable (this is an open-label study with a single treatment arm).

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 with study drug will be calculated by the sponsor based on participant responses in the eDiary about study drug application.

Participants will be instructed to bring all empty, partially used, and unused tubes of study drug with them to the study visits in order for site personnel to confirm usage of the study drug.

6.5. Dose Modifications

No application adjustments/modifications (decrease or increase in study drug strength or frequency of application) are allowed during the study.

The only modifications to the treatment regimen are either temporary interruption or permanent withdrawal of the study drug (eg, for management of an AE).

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

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

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

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

Table 7: Guidelines for Interruption and Restarting of Treatment Applications if Adverse Event is Deemed Related to Study Drug

Adverse Event Related to Study Drug[a]	Action Taken
ANC < 750/µL (without fever); < 1000/µL (with fever)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.
Any other Grade 3 laboratory abnormality (eg, hemoglobin with the exception of asymptomatic elevations in triglyceride, cholesterol, or amylase)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.
Any Grade 4 laboratory abnormality or AST or ALT (> 20 × ULN)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Discontinue study drug if lab abnormalities are confirmed.

[a] In the opinion of the investigator.

6.5.2. Criteria for Permanent Discontinuation of Study Drug

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

- Occurrence of an AE that is related to treatment with 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.
- Participant presents with a worsening of AD that requires treatment with a prohibited concomitant medication.
- Persistent AE requiring a delay of therapy for more than 2 weeks without resolution of the AE.

See Section 7 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study drug and within 30 days after the last dose of study drug will be recorded in the eCRF.

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

6.6.1. Permitted Medications and Procedures

The following are permitted during the study:

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

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Use of any over-the-counter, nonprescription preparations or prescription medications deemed acceptable by the investigator are permitted under an established and stable treatment regimen (as long as not otherwise prohibited under this Protocol).
- Allergen immunotherapy (desensitization) is not recommended during the study unless deemed necessary by the investigator.
- Bleach baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
- Participants should not take baths or showers within 2 hours after study drug application.
- Topical anti-infectives or other topical treatments applied to active AD lesions should not be used for at least 4 hours before and 2 hours after application of study drug.

6.6.3. Prohibited Medications and Procedures

Refer to the study exclusion criteria (Section 5.2) for the full list of medications (and their required washout duration) that are prohibited during the study, which include, but are not limited to, the following:

- Prescription medication for sleep or over-the-counter sleep aids (including H1 sedating antihistamines)
- Hypnotics (prescribed or over-the-counter)
- Melatonin
- Valerian
- Nonstimulant diet pills
- Barbiturates
- Benzodiazepines
- GABA analogues
- Hydantoins
- Phenyltriazines
- Antihistamines (centrally-acting H1, including over-the-counter) with known sedating effects; nonsedating antihistimines (eg, Claritin™) are not prohibited
  - Diphenhydramine HCl
  - Carbinoxamine
  - Doxylamine
  - Dimenhyrinate
  - Triprolidine
  - Bromopheniramine
  - Chlorphemamine
  - Hydroxyzine
- Anxiolytics with known sedating effects
  - Lorazepam
  - Alprazolam
  - Buspirone
- Stimulants
  - Amphetamines
  - Modafinil
  - Armodafinil
  - Methylfenidate
  - WAKIX (pitolisant)
  - Sunosi (solriamfetol)
- Herbal preparations with sedating effects
- Any investigational medication other than the study drug, including systemic or other topical JAK inhibitors.
- Topical corticosteroids, tacrolimus, pimecrolimus, and PDE-4 inhibitors (Eucrisa®)
- Other topical agents for AD (except bland emollients as noted in Section 6.6.1).
- Treatment known to affect the course of AD.

- Systemic corticosteroids, methotrexate, cyclosporine A, azathioprine and biological therapies, or other immunosuppressant agents.
- Phototherapy or tanning beds
- 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.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety monitoring.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Any AE of unacceptable severity as noted in Section 6.5.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Major changes to individual sleep pattern (eg, acute sickness, hospitalization, surgery, family emergency, unplanned vacation, etc) or travel plans that would interfere with sleep assessment during the study.
- Device malfunction or other reason that would interfere with sleep data collection during the 7 days prior to baseline (ie, during Day −7 to Day -1) or prior to the Week 8 visit (ie, during Day 49 to Day 56).
- The participant's AD worsens during the treatment period to an extent that, in the opinion of the investigator, it requires treatment with study drug over an area exceeding 20% BSA.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study drug/treatment administration in the investigator's opinion, the 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 ET visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit (see Table 3 and Table 4). The last date of the last application 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 and the primary reason for discontinuation must be included in the eCRF.
- The ET visit should be performed and date recorded in eCRF.
- Participants must be followed for safety until the time of the follow-up visit or until study drug-related AEs resolve, return to baseline, or are deemed irreversible, whichever is longest.
- [redacted]

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

7.2. Participant Withdrawal From the Study

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

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

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to 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 their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. An ICF template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent 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 their personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF (if rescreened > 42 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 and the day the participant is enrolled in the study (first day of the treatment period). Informed consent must be obtained before performing any study-specific procedures. The screening period may not exceed 42 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process, including collecting 7-day averages of the number of hours the participant sleeps at night during the screening and pretreatment sleep assessments.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before the treatment period will be used to determine eligibility. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, after recovery from an infection); however, participants who do not meet the criteria for the Itch NRS score, PROMIS Sleep Disturbance – Short Form 8b score, and TST requirements (determined using data from the Ōura Ring wearable device [redacted] wireless device) during screening may not be rescreened. The participant is not required to sign another ICF if the rescreening occurs within the participant's screening period (which may be up to 42 days in duration, depending on medications a participant is taking that require a washout) from the previous ICF signature date.

During the screening period, participants will washout any AD treatments or other excluded treatments. The screening sleep assessment may occur during or after this washout; the pretreatment sleep assessment will occur after completion of the washout.

See Section 5.4 for information regarding screen failures and the rescreening procedure for participants. See Section 5.5 for information regarding replacement of participants.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT system to obtain the participant ID number during screening.

Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study medication assignment. Additionally, the IRT system will be contacted at each clinic visit (see Table 3) to update the study drug supply. The IRT system will also be used, during the study visits, to recalculate the amount of study drug to be dispensed if the participant's %BSA of AD lesions to be treated has changed. In addition, the IRT system will be utilized to distribute the wireless and wearable sleep monitoring devices. Additional details are provided in the IRT Manual.

8.1.4. Visit Reminders and Distribution of eDiary and Sleep Monitoring Devices

Participants will be provided with a reminder notification indicating the date/time of the next visit.

At screening, participants will be issued a handheld device (eDiary) to complete PROs (see Section 8.3) and to record application of study drug. Each participant will be provided

instructions for completing the diary from screening through Week 8 or treatment discontinuation. Compliance with the eDiary will be assessed electronically at the visits noted in the SoA (see Table 3). If the participant is not completing the eDiary frequently enough, the site staff will be informed so compliance can be addressed in a timely manner.

Study sites will contact participants 1 week before the baseline visit to confirm compliance with eDiary assessments. Detailed directions for the administration of the eDiary will be provided in the Study Manual.

During screening, participants will also be provided with a wearable device (Ōura Ring) and a [redacted] (see Section 8.2.1). It may take up to 7 days during the screening period for the devices to be installed and/or configured and ready for sleep monitoring.

8.1.5. Demography and Medical History

8.1.5.1. Demography and General Medical History

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

8.1.5.2. Medical and Treatment History

Relevant medical and treatment history for the past year will be collected at screening by the investigator or qualified designee. Details regarding the participant's current and history of AD and any comorbid sleep-related disorders, including date of diagnosis, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded. A medical history of other conditions related to AD will also be collected at this time.

8.2. Efficacy Assessments

8.2.1. Health Economics

Health economic parameters are not evaluated in this study.

8.2.2. Monitoring Sleep

Sleep patterns of participants enrolled in the study will be monitored during the screening period recording, or GPS capabilities. The mobile device application does not collect any additional data outside of the required data for this study.

[redacted]

During the screening period, the participant will be provided with an Ōura Ring wearable device, which will be used initially to determine the degree of sleep disturbance during the screening sleep assessment (ie, to confirm the participant meets the eligibility requirement for a 7-day average TST ≤ 6.5 hours/night). If the 7-day average TST during the screening sleep assessment is > 6.5 hours/night and the participant was undergoing a washout for AD treatments or other excluded treatments at the time, the participant may continue to monitor sleep for up to an additional 7 days while not on medication as part of the eligibility assessment.

Participants who have a 7-day average TST ≤ 6.5 hours/night during the screening sleep assessment and who meet all other inclusion criteria and none of the exclusion criteria will then [redacted]

The sponsor of the study will not receive any identifiable data from either device. No identifiable data will be reported as a part of the study results. The participant ICF will include details of device functionality, data collected, and intended use of the data. Both devices will report sleep-related measurements: TST, [redacted]

8.2.2.1. Total Sleep Time

Total sleep time is the total amount of time spent during a planned sleep episode. Participants with AD may experience reduced TST due to episodes of awakening due to itching. Decreased TST is indicative of increased sleep disturbance. A treatment alleviating itch among participants with AD may increase TST.

[redacted]

[redacted]

[redacted]

[redacted]

8.2.3. Investigator's Global Assessment

IGA is an overall eczema severity rating on a 0 to 4 scale that will be assessed during site visits as outlined in the SoA (see Table 3). The severity strata for the IGA are shown in Table 8.

Table 8: Investigator's Global Assessment

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

Source: www.homeforeczema.org

8.2.4. Body Surface Area

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

Participants must have BSA involvement (excluding scalp) of 3% to 20% to be eligible for the study.

8.2.5. Photography of Target Lesion

Photography of the participant's target lesion will be performed as outlined in the SoA (see Table 3). On Day 1, the photographs will be taken at the clinic site, and after Day 1, participants will take photographs of the same lesion at home weekly up to Week 8 (the Week 8 photographs may be taken by the participant at home prior to the visit or may be taken at the clinic site during the visit).

The target lesion will be selected by the investigator at the Day 1 (baseline) visit and should be at least 5 cm^2 in size. Photographs will be taken via 2 views (close-up and regional body area) throughout the treatment period, even if the AD lesion has cleared or disappeared. A note should be made in the participant's source documents of the target lesion location, and the photographs can be marked with the location of the target lesion at each visit.

Participants will be instructed to avoid taking pictures of areas that may lead to the identification of the participant (eg, face). Any pictures that may include identifiable information will be de-identified prior to the investigator accessing the pictures. The participants will be encouraged to take pictures more frequently than required.

Participants will be provided with a device (eg, the eDiary) that is equipped with a camera capable of taking photographs. Participants will be instructed to take each picture with the same consistency (background, lighting, etc). De-identified pictures will be stored in a secure server and will be used to demonstrate the effectiveness of the treatment using a visual medium.

8.3. Patient-Reported Outcomes

The frequency of collection for each PROs is specified in the SoA (see Table 3).

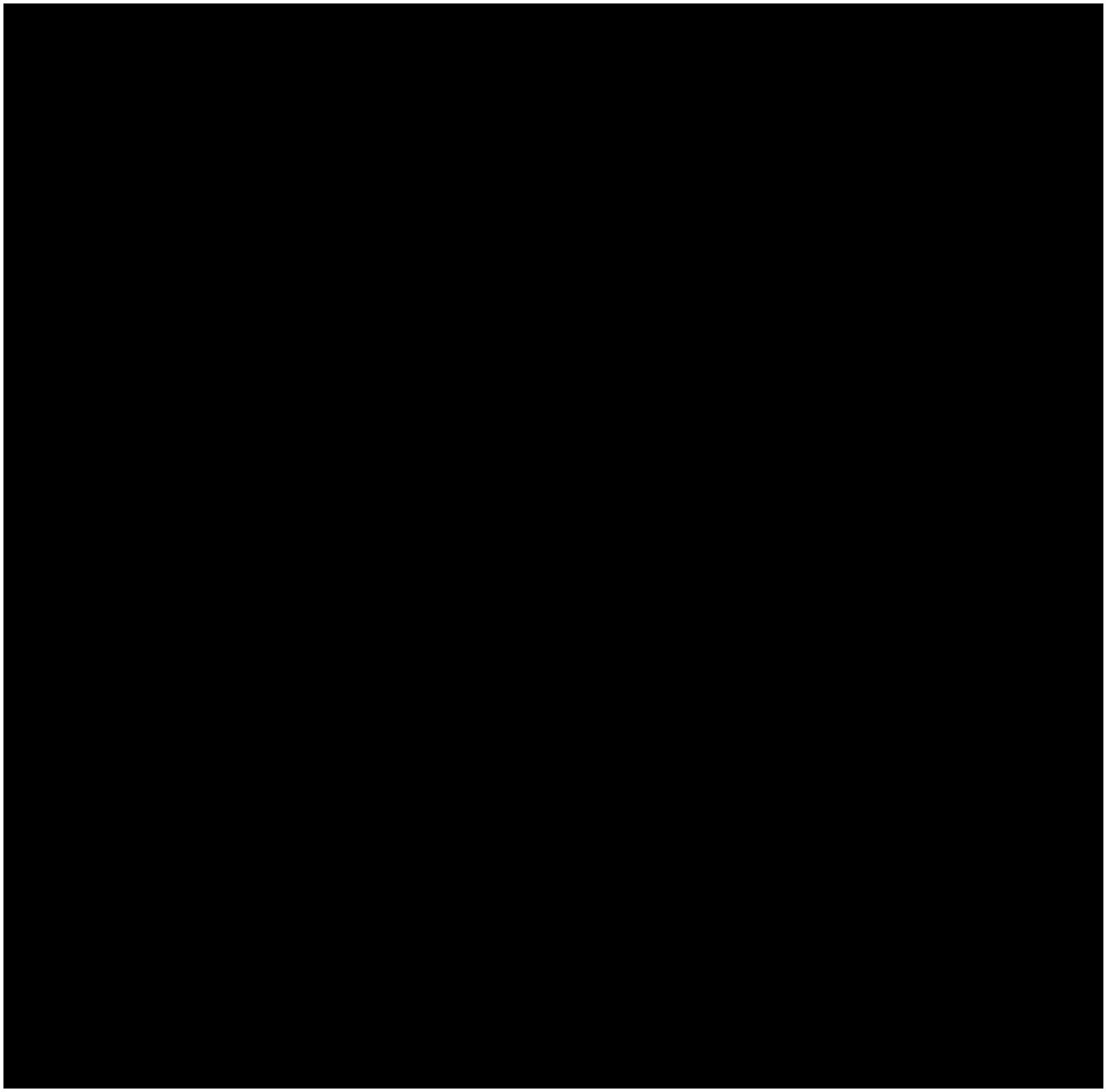
The 4 questions comprising the STOP portion of the STOP-BANG (see Section 8.3.1) questionnaire will be completed as part of the screening assessment. The following other PROs will be completed by the participants at home using an eDiary that will be issued at the time of screening.

- [redacted]
- [redacted]

8.3.1. STOP Criteria for High-Risk Obstructive Sleep Apnea

The STOP criteria from the STOP-BANG questionnaire will be administered during screening to determine if a participant is at high risk for obstructive sleep apnea. Participants answering "Yes" to all 4 questions below will not be enrolled into the study:

1. Do you snore loudly? (Louder than talking or loud enough to be heard through closed doors)
2. Do you often feel tired, fatigued, or sleepy during the daytime?
3. Has anyone observed you stop breathing during sleep?
4. Do you have (or are you being treated for) high blood pressure?



[redacted]

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Table 3).

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

8.4.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last application of study drug. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study 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, that are 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).

8.4.2. Physical Examinations

Physical examinations will be conducted at the timepoints listed in the SoA (see Table 3).

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessments of the following organ or body

systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

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

Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.3. Vital Signs

Vital signs will be collected at the time points listed in the SoA (see Table 3).

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the sitting position after 5 minutes of rest. Height and weight will also be assessed at screening.

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

8.4.4. Laboratory Assessments

See Table 9 for the list of clinical laboratory tests to be performed and Table 4 for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, and urinalysis). Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

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

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

Table 9: Required Laboratory Analytes

Blood Chemistries	Hematology	Serology
• Albumin • ALP • ALT • AST • Bicarbonate or CO_2 • Blood urea nitrogen or urea • Calcium • Chloride • Creatine kinase • Creatinine • Glucose • Lactate dehydrogenase • Phosphate • Potassium • Sodium • Total bilirubin • Direct bilirubin (if total bilirubin is elevated above 1.5 × ULN) • Total protein	**Complete blood count, including:** • Hemoglobin • Mean corpuscular volume • Hematocrit • Platelet count • Mean platelet volume • In samples with abnormalities in platelet count or size distribution (as indicated by an automated analyzer), a blood film should be examined. • Red blood cell count • Red blood cell distribution width • WBC count **Differential count (% and absolute values), including:** • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	• HIV antibody **Pregnancy Testing** Women of nonchildbearing potential will have FSH tested at screening. Women of childbearing potential will require the following: • Serum pregnancy test at screening. • Urine pregnancy test at all other in-clinic visits and as medically indicated or per country or institutional requirements. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

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

8.4.4.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening. Urine pregnancy tests will be performed locally as outlined in Table 4, and as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected). If a urine pregnancy test is positive, the results must be confirmed with a serum pregnancy test.

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

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

8.4.4.2. Serology

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

8.5. Pharmacokinetic Assessments

There is no plan to assess pharmacokinetic parameters in this study.

8.6. Pharmacodynamic and Translational Assessments

Pharmacodynamic parameters are not evaluated in this study.

8.7. Unscheduled Visits

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

8.8. End of Treatment and/or Early Termination

If a decision is made that the participant will permanently discontinue study drug, then the ET visit should be conducted. If the ET visit coincides with a regular study visit, then the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET page in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the ET procedures completed. The participant should be encouraged to return for the follow-up visit.

8.9. Follow-Up

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT (Week 8) visit (or ET visit, if applicable) and the scheduled follow-up visit, which should occur 30 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the

follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

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

9.1. Definition of Adverse Event

Adverse Event Definition
• 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, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study 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 dose administration errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy" or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • 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 Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant ID 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 final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event.
  Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures, and Non-Drug Therapy).

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study 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 for study drug in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Once an AE is detected, it should be followed in the Adverse Events Form in the 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.
- New or updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax if paper SAE form is used or in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

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

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study drug or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the ruxolitinib cream IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF.
- The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Manual.

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study 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 evaluations. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study 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 and reported as described in Section 9.4.

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

9.8. Warnings and Precautions

Special warnings or precautions for the study 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.

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

9.9. Product Complaints

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

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

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

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

9.10. Treatment of 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

All participants will receive treatment with ruxolitinib cream 1.5% BID. The primary analysis will compare the difference in TST between baseline and Week 8 (see Section 10.4.1). If the true increase in TST is 30 minutes, a sample size of 70 participants will provide > 90% power to reject the null hypothesis at $\alpha = 0.05$. Accounting for loss to follow-up and device malfunction, a total of 100 participants will be enrolled into the study.

10.2. Populations for Analysis

The populations for analysis are provided in Table 10. The primary analysis will be performed in the PP population.

Table 10: Populations for Analysis

Population	Description
STP	The STP is defined as study eligible participants who received at least 23 applications in any interval of 14 consecutive days of study drug administration BID (ie, participants with ≤ 5 missed applications out of 28 in any 14-day interval across the 8-week treatment period are included).
PP	The PP population includes all participants in the STP population who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who received at least 1 application of study drug during the treatment period.

10.3. Level of Significance

The hypotheses for the primary and secondary endpoints (Section 10.4) will be tested at level of significance 0.05. All analyses described in primary, secondary, and exploratory objectives will be conducted and will be assessed at 0.05 level of significance. No adjustments for multiple testing will be performed.

10.4. Statistical Analyses

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

10.4.1. Sleep Assessment Endpoints

The following endpoints will be evaluated to determine reduction in sleep disturbance:

- TST: The total amount of time spent during a planned sleep episode
- [redacted]

The baseline assessments of sleep will be determined as the average of the 7 days prior to Day 1. Participants with data for at least 4 days out of the 7 days prior to Day 1 will be included in the analysis. The Week 4 and Week 8 sleep assessments will be determined using the average of the sleep measurements during the 7 days prior to Week 4 (Day 21 to Day 28) and Week 8 (Day 49 to Day 56), respectively. Participants with at least 4 days of sleep measurements during Week 4 and Week 8 assessment periods will be included in the analysis. The number of days with available data will be used to calculate the average for the week. The reduction in sleep disturbance will be calculated as the difference between the sleep assessment measures between Week 8 and baseline assessments.

10.4.2. Primary Analysis

The primary endpoint of the study is change from baseline in mean TST as measured by Ōura Ring wearable device at Week 8. A paired t-test will be used to test the hypothesis below for participants with both TST measurements at baseline (as determined during the pretreatment sleep assessment) and Week 8 (Day 49 to Day 56):

H_0: $TST_{(Week\ 8)} - TST_{(Baseline)} = 0$

H_1: $TST_{(Week\ 8)} - TST_{(Baseline)} \neq 0$

Mean, standard deviation, 95% confidence interval of TST at each evaluable timepoint will be presented. Mean pair-wise difference and 95% confidence interval of the difference will be presented. The hypotheses above will be tested at level of significance 0.05. The primary analysis will include participants with both baseline and Week 8 TST assessments available. Missing data imputation (LOCF) may be considered as a sensitivity analysis.

10.4.3. Secondary Analysis

The secondary endpoint is the PROMIS Sleep Disturbance – Short Form 8b score. A paired t-test will be used to test the hypothesis below for participants with PROMIS Sleep Disturbance – Short Form 8b score at both baseline and Week 8.

H_0: PROMIS Sleep Disturbance – Short Form 8b score $_{(\text{Week 8})}$ – PROMIS Sleep Disturbance – Short Form 8b score $_{(\text{Baseline})} = 0$

H_1: PROMIS Sleep Disturbance – Short Form 8b score $_{(\text{Week 8})}$ – PROMIS Sleep Disturbance – Short Form 8b score $_{(\text{Baseline})} \neq 0$

Mean, standard deviation, and 95% confidence interval of overall sleep score at each evaluable timepoint will be presented. Mean pair-wise difference and 95% confidence interval of the difference will be presented. The hypotheses above will be tested at level of significance 0.05. The secondary analysis will include participants with both baseline and Week 8 PROMIS Sleep Disturbance – Short Form 8b scores available. Missing data imputation (LOCF) may be considered as a sensitivity analysis.

10.4.4. Exploratory Analysis

[redacted]

10.4.5. Safety Analyses

Safety analyses will be conducted for the safety population.

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE 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 quantitative variables (eg, laboratory assessments, vital signs [blood pressure, pulse, respiratory rate, and body temperature]) at each assessment time.

10.4.6. Ad Hoc and Post Hoc Analyses

Additional ad hoc and/or post hoc analyses including, but not limited to, assessing the association between different sleep assessment measures, the association between PROs and sleep assessment measures, changes in additional sleep-related metrics reported by wearable and

wireless devices, etc may be conducted upon completion of the primary analysis. All ad hoc and post hoc analyses will be documented in a separate ad hocSAP.

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.

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

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

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

The investigator will be responsible for the following:

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

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

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Data from the wireless and wearable devices will not be integrated into the eCRFs. The data from the wireless and wearable devices will be directly integrated into the study database.

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 monitoring plan.

Quality tolerance limits will be predefined in the operational manual subsection (or equivalent) to identify systematic issues that can impact participant's safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the QTLs and remedial actions taken, including reporting to IRBs/ECs if applicable, will be summarized in the clinical study report.

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. Appropriate notice, or notice and consent (as may be required for 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.

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.

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

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

11.7. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

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

For male participants of reproductive potential[b]

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

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

The following are not acceptable methods of contraception:

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

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

For female participants who are WOCBP
The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[d] – oral • Progestogen-only hormonal contraception associated with inhibition of ovulation[d] – oral – injectable – implantable[e] • Intrauterine device[e] • Intrauterine hormone-releasing system[e] • Bilateral tubal occlusion[e] • Vasectomized partner[e,f] • Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[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 Group 2020.

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Number of Study Participants

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

Study Visits

If there are local travel restrictions, isolation requirements, or the investigator determines it to be unsafe for participants to attend the participant's scheduled study visit, the site staff may conduct the visit via telemedicine (phone or video calls) to minimize participant risk as follows:

- **Screening Period:**
  - The screening visit must be performed in person.
- **Treatment Period:**
  - The Day 1/baseline visit must be performed in person. If the baseline visit cannot be performed on-site at the end of the 7-day pretreatment sleep assessment, the participant will be considered to have failed screening. Participants who screen failed due to COVID-19 may be rescreened at a later time, if feasible.
  - The Week 4 and Week 8/EOT/ET visits must be performed in person.
- **Safety Follow-Up Period:**
  - The follow-up visit may be conducted via telemedicine, if necessary.
- **Telemedicine Visits:**
  - At a minimum, a review of AEs, concomitant medications, and study drug application compliance must be completed and recorded in the EDC.
  - No BSA assessments can be performed even if the telemedicine visit is a video call or photography of the active lesion areas are provided.
  - Patient reported outcomes measurements recorded in the eDiary should be completed as scheduled prior to the telemedicine visit, but collected at the next on-site visit of the participant.
  - All assessments not performed will be recorded in the EDC as Protocol deviations and reason documented as COVID-19.

Investigational Medicinal Product Dispensation and Distribution

In the event a participant is not be able to attend an on-site study visit due to COVID-19, and in order to ensure the continuity of providing participants' clinical supplies within the constraints imposed by the pandemic, the site staff may decide to supply study treatment to participant as follows:

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

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution as detailed in the Data Monitoring Guidelines. If allowed by local regulations, remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

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

Direct Contracts with Third Parties/Specialized Service Companies

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

Reimbursement of Extraordinary Expenses

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

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.

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