Official Title: A Phase 2, Double-Blind, Randomized, 16-Week, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Open-Label Extension Period in Adults With Chronic Hand Eczema

NCT Number: NCT05906628

Document Date: Protocol INCB 18424-226 Am 1 Version 2 19 APR 2023

Clinical Study Protocol

INCB 18424-226

A Phase 2, Double-Blind, Randomized, 16-Week, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Open-Label Extension Period in Adults With Chronic Hand Eczema

Product:	**INCB018424**
IND Number:	**77101**
EU CT Number:	**2022-502827-23-00**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**12 DEC 2022**
Protocol Amendment 1:	**19 APR 2023**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Brazil 2013) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study is being conducted.

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-226 Protocol Amendment 1 (dated 19 APR 2023) 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
ACD	allergic contact dermatitis
AD	atopic dermatitis
AE	adverse event
AHE	atopic hand eczema
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CHE	chronic hand eczema
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBVC	double-blind vehicle-controlled
DLQI	Dermatology Life Quality Index
EDC	electronic data capture
eDiary	electronic diary
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HE	hand eczema
HECSI	Hand Eczema Severity Index
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	irritant contact dermatitis
ICD-10	International Classification of Diseases, 10th Revision
ICD-11	International Classification of Diseases, 11th Revision
ICF	informed consent form

Abbreviations and Special Terms	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-CHE	Investigator's Global Assessment–Chronic Hand Eczema
IGA-CHE-TS	Investigator's Global Assessment–Chronic Hand Eczema Treatment Success
IGA-TS	Investigator's Global Assessment–Treatment Success
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
OLE	open-label extension
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
QALY	quality-adjusted life-year
QOLHEQ	Quality of Life in Hand Eczema Questionnaire
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
STAT	signal transducers and activators of transcription
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
Th	T-helper
TYK	tyrosine kinase
ULN	upper limit of normal
VAS	visual analog scale
WOCBP	woman of childbearing potential
WPAI-ChHD	Work Productivity and Activity Impairment Questionnaire v2.0 in Chronic Hand Dermatitis

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Double-Blind, Randomized, 16-Week, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Open-Label Extension Period in Adults With Chronic Hand Eczema

Protocol Number: INCB 18424-226

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with CHE.	• IGA-CHE-TS[a] at Week 16.
Key Secondary	
To further assess the treatment effects of ruxolitinib 1.5% cream BID in participants with CHE.	• ITCH4[b] response at Week 16. • ITCH4 response at Week 4. • ITCH4 response at Week 1 (Day 7).

[a] IGA-CHE-TS is defined as an IGA-CHE score of 0 or 1 with ≥ 2-grade improvement from baseline.
[b] ITCH4 response is defined as a ≥ 4-point improvement in CHE-related Itch NRS score from baseline.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Treatment of adult patients with moderate to severe CHE (IGA-CHE score of 3 or 4).
Population	Male and female participants ≥ 18 years of age with diagnosis of CHE for at least 6 months who have moderate to severe disease activity (IGA-CHE score of 3 or 4) and have been treated with at least 1 prescription CHE therapy.
Number of Participants	Approximately 180 participants will be randomized 1:1 to 1 of 2 treatment groups (ruxolitinib 1.5% cream BID or vehicle cream BID). The participants will be stratified by IGA-CHE score (3 or 4) at baseline and by region (North America or outside of North America).
Study Design	This is a randomized, 16-week, double-blind, vehicle-controlled study with a 16-week open-label treatment extension.

Table 2: Key Study Design Elements (Continued)

Estimated Duration of Study Participation	Estimated total duration of participants is up to approximately 40 weeks. • Screening: up to 4 weeks • DBVC period: 16 weeks • OLE period: 16 weeks • Safety follow-up: 30 days
Data Safety Monitoring Board/Data Monitoring Committee	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

Approximately 180 adult participants with moderate to severe CHE with no history of (within the past 5 years) or current AD will be randomized 1:1 to either ruxolitinib 1.5% cream BID or vehicle cream BID (see Figure 1). During the DBVC period, participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) to CHE-affected areas on the hands and wrists (if applicable) for 16 weeks. All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 16) unless the participant meets criteria for stopping study drug (see Section 7.1).

At Week 16, participants with no safety concerns will enter the 16-week OLE period, during which all participants will receive open-label ruxolitinib 1.5% cream. Affected areas will be treated as needed until they clear during the OLE period (see Section 6.1). Participants, investigators, and the sponsor will be blinded to each participant's treatment assignment during the DBVC period. During the OLE period, participants and investigators will remain blinded to the treatment assignment during the DBVC period until after all participants have completed treatment or discontinued and completed the safety follow-up period.

Participants who develop additional areas of CHE may treat the additional areas with approval by the investigator as long as there are no safety concerns regarding the application of study drug.

Table 3 presents the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The COVID-19 global pandemic may present challenges to the normal conduct of this study (including AE and laboratory assessments), requiring the outline of potential mitigation strategies described in Appendix B.

Figure 1 presents the study design schema.

Figure 1: Study Design Schema

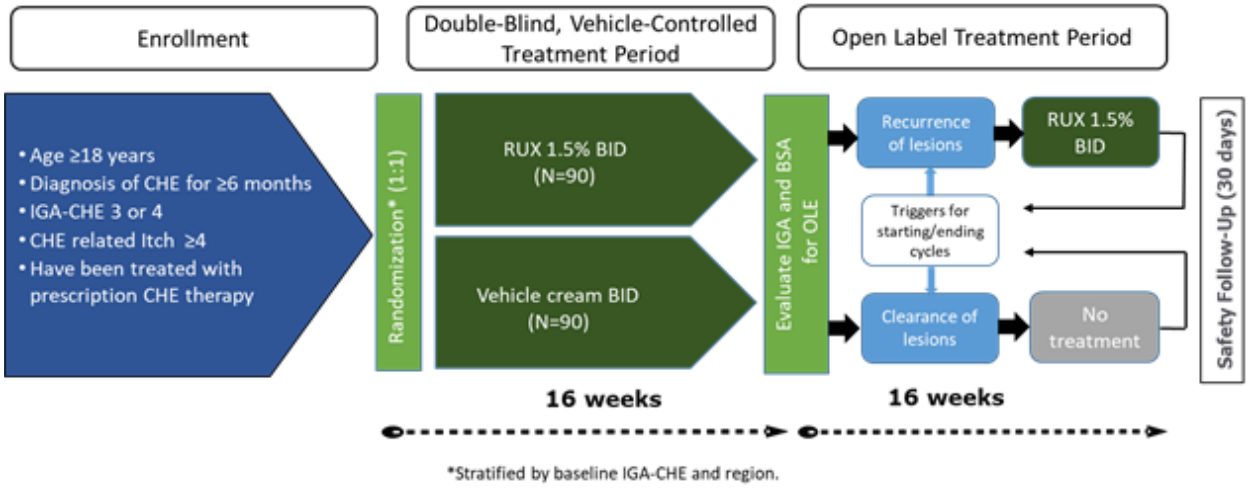


Table 3: Schedule of Activities

Visit Day (Range)	Days −28 to −1	Vehicle-Controlled Treatment						Open-Label Treatment		Safety Follow-Up	Notes
		Day 1	Weeks					Weeks		Days	
	Screening	Baseline	2[a] (± 3 d)	4 (± 3 d)	8 (± 3 d)	12[a] (± 3 d)	16[b]/ET1 (± 3 d)	24[a] (± 3 d)	32/ET2[c] (± 3 d)	30[a,d] (+ 7 d After Last Application)	
Administrative procedures											
Informed consent	X										
Contact IRT	X	X	X	X	X	X	X	X	X	X	
Inclusion/exclusion criteria review	X	X									
Demography and medical history (general and disease specific)	X										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	
Apply study drug in clinic*		X	X	X	X	X	X	X†			*On-site applications will be performed by participants. The application will be under supervision at baseline but not mandated for subsequent visits. †No study drug will be applied at Week 24 if BSA is 0 at the visit.
Distribute reminder card		X	X	X	X	X	X	X	X		
Weigh/dispense study drug		X	X	X	X	X	X	X			
Collect/weigh returned study drug			X	X	X	X	X	X	X		
Assess eDiary and study drug compliance	X*	X†	X	X	X	X	X	X	X		*At screening, eDiary will be issued and compliance check is not needed. eDiary for Itch and Skin Pain NRS is to be started at screening, and compliance should be checked starting at baseline. †eDiary for study medication is to be started at baseline, and compliance should be checked starting with the following visit.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Days −28 to −1	Vehicle-Controlled Treatment						Open-Label Treatment		Safety Follow-Up	Notes
		Day 1	Weeks					Weeks		Days	
	Screening	Baseline	2[a] (± 3 d)	4 (± 3 d)	8 (± 3 d)	12[a] (± 3 d)	16[b]/ET1 (± 3 d)	24[a] (± 3 d)	32/ET2[c] (± 3 d)	30[a,d] (+ 7 d After Last Application)	
Safety assessments											
AE assessments	X	X	X	X	X	X	X	X	X	X	If an AE is noted, that body system should be physically examined in a targeted physical examination.
Comprehensive physical examination	X*						X†		X		*Including Fitzpatrick skin classification. †Only required for participants not continuing in the OLE period.
Height and body weight	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	
Efficacy assessments											
%BSA	X	X	X	X	X	X	X	X	X	X	The %BSA affected by CHE only (including hands and wrists [if applicable]).
Target lesion		X*			X		X				*At select study sites participating in skin sampling for biomarker collection, a target lesion will be identified at baseline on a hand affected by CHE.
IGA-CHE	X	X	X	X	X	X	X	X	X	X	
HECSI		X	X	X	X	X	X	X	X	X	
Photography		X		X	X		X	X	X		Photographs of the hand and wrist (anterior and posterior) will be taken at all study sites. At select sites, photographs will be marked with the location of the target lesion and nonlesional area at the baseline visit.
CHE-related Itch NRS	X*	Diary is completed each evening from screening through Week 32 or ET.									*Average of 7-day (minimum 4/7 days) CHE-related Itch NRS directly prior to Day 1 will be used to determine study eligibility.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Days −28 to −1	Vehicle-Controlled Treatment						Open-Label Treatment		Safety Follow-Up	Notes
		Day 1	Weeks					Weeks		Days	
	Screening	Baseline	2[a] (± 3 d)	4 (± 3 d)	8 (± 3 d)	12[a] (± 3 d)	16[b]/ET1 (± 3 d)	24[a] (± 3 d)	32/ET2[c] (± 3 d)	30[a,d] (+ 7 d After Last Application)	
Efficacy assessments (continued)											
CHE-related Skin Pain NRS	X	Diary is completed each evening from screening through Week 32 or ET.									
DLQI		X	X	X	X	X	X	X	X		
PGIC			X	X	X	X	X	X	X	X	
QOLHEQ		X	X	X	X	X	X	X	X	X	
EQ-5D-5L		X	X	X	X	X	X	X	X		
WPAI-ChHD		X	X	X	X	X	X	X	X	X	
Laboratory assessments											
Chemistry assessments	X	X*			X		X	X	X	X	*Not necessary if screening assessment performed within 14 days of Day 1.
Hematology assessments	X	X*			X		X	X	X	X	
FSH	X*										*Women of nonchildbearing potential only.
Serum pregnancy test	X										WOCBP will have a serum test at screening and a urine test at other visits noted. A positive urine test must be confirmed by a serum test.
Urine pregnancy test		X		X	X	X	X	X	X	X	
HIV serology	X										
PD and translational assessments											
[redacted]		[redacted]			[redacted]		[redacted]				[redacted]
[redacted]		[redacted]			[redacted]		[redacted]				[redacted]

[a] Visits at Weeks 2, 12, and 24 and safety follow-up can be performed virtually (through telemedicine if applicable) only due to COVID-19–related reasons. No efficacy assessments can be performed virtually (see Appendix B).
[b] All Week 16 assessments must be completed before the participant can continue in the OLE. Study drug will not be applied in the clinic at Week 16 for participants not continuing into the OLE period.
[c] Participants who withdraw early should complete the ET and the safety follow-up visits.
[d] For participants in the OLE period who have been in an observation/no treatment cycle with a total IGA-CHE score of 0 (clear) from Week 28 or earlier until Week 32, the Week 32/ET visit will also count as the safety follow-up visit.

2. INTRODUCTION

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for a variety of dermatological conditions. Ruxolitinib 1.5% cream is approved by the US FDA for 1) 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 and 2) the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older (Opzelura™ 2022). Ruxolitinib phosphate is a JAK1/2 inhibitor. The JAK/STAT pathway mediates the effects of many inflammatory cytokines that are implicated in the pathogenesis of a number of inflammatory dermatosis (Chapman et al 2022).

2.1. Background

2.1.1. Chronic Hand Eczema Disease

Hand eczema is a common disorder involving inflammation of the skin of the hands. The clinical manifestations of HE typically present in an acute (lasting for < 3 months and not occurring more than once per year) or chronic (lasting for > 3 months or recurring at least 2 times within a year) fashion (Diepgen et al 2015), with severity varying from mild to severe (Agner and Elsner 2020). Clinical signs include redness, thickening of the skin, scaling, edema, vesicles, areas of hyperkeratosis, and cracks (fissures). During the acute stage, HE usually presents with macules, papules, erythema, edema, weeping, and vesiculation. As lesions become subacute or chronic, the lesion morphology shifts to scaling, thickening, and fissuring of the skin. Lesions are usually bilateral and may involve the palmar or dorsal surface or both and/or the fingers. In long-standing disease, nail changes may be seen, including loss of the cuticle, thickening of the nail folds, ridging, and thickening of the nail plate. Symptoms typically include pruritus, burning, pain, stinging, sleep disturbances, and/or mood disturbances (Agner and Elsner 2020).

2.1.2. Population

The prevalence of HE and CHE is greater in the adult population than in the pediatric population. Hand eczema is common in the adult population (4%), with a 1-year prevalence of approximately 10% (Coenraads 2012) and a lifetime incidence of 15% (Thyssen et al 2010). An estimated < 5% of patients with HE develop chronic disease, and about one-half of these cases are steroid refractory (Crane et al 2017). Limited data exist regarding the epidemiology of chronic HE in the pediatric population. A study in the United Kingdom leveraging data from the Clinical Practice Research Datalink reported that HE is relatively uncommon (0.2%) in children younger than 18 years of age and CHE is extremely rare (0.004%) in children up to the age of 14 years in 1-year prevalence (Crane et al 2017). Furthermore, the 10-year prevalence for CHE estimates near zero in children younger than the age of 14 years. The prevalence of CHE in late adolescence (15-19 years of age) is approximately 0.05%, increasing by the third decade (approximately 0.2%), maintaining this level throughout the occupational years, and declining in the eighth decade (Crane et al 2017).

Chronic HE is often an occupational skin disease. While some patients with CHE may also have AD, the cause of CHE is considered multifactorial and distinct from AD in most patients.

Individuals with occupational HE develop contact dermatitis on the hands and/or wrists due to exposure to irritants (up to 70% of cases) and/or allergens (up to 25% of cases) in the workplace (Agner et al 2015, Agner and Elsner 2020, Caroe et al 2014, Diepgen et al 2009, Menné et al 2011). This has a significant professional impact, leading to > 20% job-related disability (Diepgen et al 2015). In addition to the occupational impact, individuals with CHE also experience poor quality of life (eg, sleep disturbances and domestic, social, and psychological impairment; Agner et al 2008, English 2010, Cortesi et al 2014).

Furthermore, continuous exposure to other irritants may lead to CHE, including household detergents, fragrances, and preservatives in hand soaps; harsh chemicals found in common household and industrial cleaners, such as ammonia and solvents; raw fruits, vegetables, spices, and plants; and physical irritants, such as cold (Agner and Elsner 2020). Similarly, HE may be a manifestation of ACD, a specific T cell–mediated, delayed-type hypersensitivity reaction. Common allergens associated with HE are preservatives, fragrances, metals (eg, nickel or cobalt), rubber, and topical antibiotics (Agner and Elsner 2020).

Hand eczema may not always be associated with AD. A meta-analysis indicated that the majority of patients with HE did not have past or current AD, although AD was associated with an increased prevalence of HE (odds ratio of 4.31 based on lifetime prevalence; Ruff et al 2018). An evaluation of 522 patients with HE in a dermatology practice found 19% of patients had past or current AD at the time of the evaluation (Veien et al 2008). Another study showed that 25% of 427 patients with HE were reported to have previous or current AD (Agner et al 2015). Collectively, the data suggest that patients with HE are distinct from patients with AD and only a subset of patients have overlapping conditions.

In the management of HE, identification and exposure avoidance to causative allergens and irritants are essential in the improvement and resolution of the condition. However, not all patients may find resolution to their condition. Patients who were originally diagnosed with ICD or ACD, in the absence of exposure to irritants or allergens, may still develop CHE (Thyssen et al 2020). Thus, individuals with CHE have a very prolonged course of disease, with an average reported duration of approximately 12 years (Anveden et al 2006). Furthermore, challenges remain in the recognition of CHE as a condition, since ICD-10 diagnosis codes only exist for ACD, ICD, and AD. In ICD-11, EA85.2 only states "dermatitis of hands" (Thyssen et al 2020). Nevertheless, after the underlying triggers (irritant and allergen) have been avoided, the persistent inflammation of CHE may require management with therapies delivered in an escalating fashion (Graham-Brown 2010). In establishing an accurate diagnosis of CHE, which excludes ICD and ACD, a detailed history and physical examination is required; if the symptoms of HE are prolonged, patch testing may be necessary.

2.1.3. Inflammatory Pathways Involved in Chronic Hand Eczema

In CHE, 3 etiologies (ie, ICD, ACD, and AHE) are associated with the progression of the HE condition, and the pathophysiology of HE may vary depending on the stage of each etiology.

- Irritant contact dermatitis has an immune profile associated with Th1/Th17. Skin exposed to irritants elicits the activation of IL-1α, IL-1β, tumor necrosis factor α, granulocyte-macrophage colony-stimulating factor, and IL-8 from keratinocytes; keratinocytes break down, promoting neutrophils and mast cell infiltrates (de Jongh et al 2008, Gittler et al 2013, Leonard and Guttman-Yassky 2019).

- The immune profile for ACD may vary, depending on the allergen. Allergens associated with fragrance and rubber have shown to elicit a Th2/Th22 response, inducing cytokines IL-5, IL-13, IL-22, IL-32, CCL5, CCL13, CCL17, CCL18, and CTLA4 (Dhingra et al 2014, Leonard and Guttman-Yassky 2019, Ungar et al 2017). Allergens such as metal have shown induction of the Th1/Th17 response, with increased expression of IL-1β, IL-6, interferon α1, CXCL1, CXCL2, CXCL9, CXCL10, and CXCL11 (Dhingra et al 2014, Leonard and Guttman-Yassky 2019, Ungar et al 2017).
- A large panel of cytokine-mediated signaling cascades have been identified as part of the immune signature of AHE, including Th1 (interferon gamma), Th2 (IL-4, IL-13, IL-31, CCL17, CCL18, and CCL22), Th22 (IL-22), Th17 (IL-17), and the JAK-STAT pathway (Brunner et al 2017, Gittler et al 2013, Leonard and Guttman-Yassky 2019, Pedersen et al 2007, Tauber et al 2020).

[redacted]

2.1.4. Current Treatment and Unmet Need in Chronic Hand Eczema

Currently, there are no FDA-approved treatments for CHE. The only approved therapy for CHE in adults is an oral retinoid (eg, alitretinoin) available in Europe, Canada, Israel, and South Korea. Thus, there is a large unmet medical need for effective and safe therapies for the management of CHE. Expert dermatologists recommend that CHE should be regarded as a chronic inflammatory disease similar to psoriasis and AD and treated with appropriate topical, systemic, and/or biologic medications after appropriate workup (Thyssen et al 2020).

Currently, the initial, nonpharmacological therapies for patients with HE include avoidance of irritants and allergens and use of hydration and emollients (Graham-Brown 2010). After the avoidance of underlying triggers (irritants and allergens), the persistent inflammation of CHE is treated with pharmacological therapies.

Individuals with mild to moderate HE are often treated with emollients and anti-inflammatory therapies including topical steroids as first-line therapy, followed by high-potency topical steroids, calcineurin inhibitors, or, in some regions/countries (Europe, Canada, Israel, and South Korea), oral retinoids (eg, alitretinoin) when topical steroids are not effective or not tolerated (Diepgen et al 2015, Dublin et al 2020, Silvestre Salvador et al 2020). Approximately 65% of patients experience a relapse or recurrent episodes after 5 years of treatment with topical agents (Agner et al 2008, Lee et al 2019). Moreover, long-term use of these therapies can result in significant side effects, including skin atrophy and barrier impairment. Individuals with moderate to severe chronic HE often become refractory to topical therapies over time.

2.2. Study Rationale

Because the pathophysiology of CHE involves inflammation mediated through the JAK-STAT pathway, the primary purpose of this study is to assess the efficacy and safety of ruxolitinib 1.5% cream BID in participants with CHE.

2.2.1. Scientific Rationale for Study Design

As mentioned in Section 2.1.2, a large panel of cytokine-mediated signaling cascades has been identified as part of the pathophysiology of CHE, including Th2 (IL-4 and IL-13), Th22 (IL-22), Th17 (IL-17), Th1 (interferon gamma), and the JAK-STAT pathway (Brunner et al 2017, Gittler et al 2013, Pedersen et al 2007). Ruxolitinib, a JAK 1/2 inhibitor, mediates its clinical effects in AD and vitiligo through many of the same cytokines that have been identified in the pathogenesis of CHE. As such, it is anticipated that ruxolitinib will have an impact on CHE.

The mechanism of ruxolitinib cream is well established in other inflammatory dermatoses (both in AD and vitiligo). Clinically, ruxolitinib cream has shown statistically significant and clinically meaningful efficacy in 2 Phase 3 registrational studies (INCB 18424-303 and INCB 18424-304) in participants with AD (including on the hands), which shares similarities with CHE (Papp et al 2021). In both Phase 3 studies of AD, more than 50% (53.8% and 51.3%, respectively) of participants (≥ 12 years of age) who applied ruxolitinib 1.5% cream BID for 8 weeks achieved an IGA-TS (defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline) compared with 15.1% and 7.6% of participants who applied vehicle cream. Participants on ruxolitinib cream also saw a substantial improvement in itch (ITCH4 response, defined as ≥ 4-point improvement from baseline in Itch NRS score) compared with vehicle in both studies (50.7% and 52.2% for ruxolitinib cream vs 16.3% and 15.4% for vehicle, respectively).

This study will examine the efficacy and safety of ruxolitinib 1.5% cream BID versus vehicle cream for the treatment of CHE. The vehicle-controlled period is 16 weeks. Participants who complete the Week 16 assessments with no safety concerns can continue into the 16-week OLE period, during which all participants will receive active treatment with ruxolitinib 1.5% cream BID to be applied as needed in affected areas. This design will provide a well-controlled assessment of the efficacy of ruxolitinib 1.5% cream in CHE compared to vehicle.

The selection of 16 weeks for the vehicle-controlled period for this study reflects the goal to balance sufficient treatment duration for an inflammatory skin condition with the need to limit the DBVC period for participants. Due to the signs of highly inflamed skin such as hyperkeratosis, vesiculations, and fissures, the time required for ruxolitinib cream to achieve treatment success in patients with moderate to severe CHE will likely be more similar to that of other moderate to severe inflammatory skin conditions such as moderate to severe plaque psoriasis and moderate to severe AD than to the 8-week treatment duration of ruxolitinib cream for mild to moderate AD. The limited data from other JAK inhibitors in clinical studies also suggest that a duration of longer than 8 weeks is necessary to achieve optimal treatment effects in CHE. For example, in the delgocitinib (a pan-JAK inhibitor with a similar mechanism of action as ruxolitinib) Phase 2a study in participants with mild to moderate CHE, maximum treatment effect was not observed at the end of the 8-week DBVC period (Worm et al 2020). In the Phase 2b study of delgocitinib cream in participants with mild to severe CHE (NCT03683719), the treatment effect had not reached a plateau at the end of treatment (16 weeks), suggesting that longer-term use could offer additional benefits than what was

observed in the trial (Worm et al 2022). The primary endpoint, change in the modified Total Lesion Symptom Score over time, indicated a rapid onset of treatment effect as early as 2 weeks that continued to increase and plateaued after 12 to 16 weeks of treatment (depending on the dose).

Therefore, a vehicle-controlled period of 16 weeks was selected for the Phase 2 study, similar to other studies involving patients with moderate to severe inflammatory skin conditions. In addition, based on the Phase 3 studies of AD (INCB 18424-303 and 304), which included treatment of up to 20% BSA during an 8-week vehicle-controlled period and a 44-week long-term safety extension period, there are no safety concerns associated with a 16-week vehicle-controlled treatment period followed by a 16-week OLE treatment extension period in the CHE studies, especially considering the limited %BSA to be treated in the CHE studies (maximum BSA is 4% if both hands are fully affected). It is also expected that the 16-week OLE period may decrease dropout rates in the vehicle arm by offering an incentive for participants to remain in the study beyond the initial 16-week DBVC period.

2.2.2. Justification for Dose

The ruxolitinib cream strength and application frequency for this study (ruxolitinib 1.5% cream BID) were selected primarily based on the following:

- Data from the dose-ranging Phase 2 study (INCB 18424-206) and 2 Phase 3 studies (INCB 18424-303 and INCB 18424-304) in participants with mild to moderate AD, in which ruxolitinib 1.5% cream BID was shown to be the most efficacious regimen evaluated. The data from these studies supported the approval of ruxolitinib 1.5% cream BID for the AD indication in the US (Opzelura 2022). Because the inflammation and hyperkeratosis associated with moderate to severe CHE is typically more severe than that observed with mild to moderate AD, [redacted] to be efficacious for treatment of CHE.
- [redacted]
- Due to the requirement to avoid hand washing, sanitizer use, or emollient use within 1 hour following study drug application and the fact that many participants are working individuals, the burden from requiring more frequent application (eg, 3 times daily) than the BID regimen that is currently specified in the Protocol would be high, impractical, and lead to decreased compliance. Less frequent application (eg, once daily) of ruxolitinib 1.5% cream is expected to be less efficacious than BID, as evident from the Phase 2 dose-ranging study (INCB 18424-206) in mild to moderate AD.

[redacted]

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with CHE.	• IGA-CHE-TS[a] at Week 16.
Key Secondary	
To further assess the treatment effects of ruxolitinib 1.5% cream BID in participants with CHE.	• ITCH4[b] response at Week 16. • ITCH4[b] response at Week 4. • ITCH4[b] response at Week 1 (Day 7).
Secondary	
To further evaluate the efficacy of ruxolitinib 1.5% cream BID.	• IGA-CHE-TS at each postbaseline visit. • ITCH4[b] response at Day 3. • Change from baseline in CHE-related Itch NRS score at each postbaseline visit. • Time to ≥ 4-point improvement from baseline in CHE-related Itch NRS score. • Change from baseline in CHE-related Skin Pain NRS score at each postbaseline visit. • Achieving ≥ 2-point improvement in CHE-related Skin Pain NRS score from baseline to Week 16. • Time to ≥ 2-point improvement from baseline in CHE-related Skin Pain NRS score. • Percentage change in HECSI from baseline to Week 16. • PGIC score at each postbaseline visit.
To evaluate the participants' quality of life and other patient-reported outcomes.	• Change from baseline in DLQI score at Weeks 2, 4, 8, 12, 16, 24, and 32. • Change from baseline in EQ-5D-5L score at Weeks 2, 4, 8, 12, 16, 24, and 32. • Change from baseline in QOLHEQ score at Weeks 2, 4, 8, 12, 16, 24, 32, and follow-up. • Change from baseline in WPAI-ChHD score at Weeks 2, 4, 8, 12, 16, 24, 32, and follow-up.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID.	• The type, frequency, and severity of AEs as well as changes in vital signs and laboratory data for hematology and serum chemistry.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

[a] IGA-CHE-TS is defined as an IGA-CHE score of 0 or 1 with ≥ 2-grade improvement from baseline.
[b] ITCH4 response is defined as a ≥ 4-point improvement in CHE-related Itch NRS score from baseline.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, double-blind, vehicle-controlled, 16-week study followed by a 16-week open-label treatment extension period. Figure 1 presents the study design schema.

Approximately 180 participants with moderate to severe CHE with no history of (within the past 5 years) or current AD will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream. Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) to CHE lesions on the hands and wrists (if applicable) for 16 weeks. All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 16) unless the participant meets criteria for stopping study drug (see Section 7.1).

At Week 16, participants with no safety concerns will enter the 16-week OLE period, during which all participants will receive open-label ruxolitinib 1.5% cream. Affected areas will be treated as needed until they clear during the OLE period (see Section 6.1).

Participants, investigators, and the sponsor will be blinded to each participant's treatment assignment during the DBVC period. During the OLE period, participants and investigators will remain blinded to the treatment assignment during the DBVC period until after all participants have completed treatment or discontinued and completed the safety follow-up period.

Participants who develop additional areas of CHE may treat these additional areas with approval by the investigator as long as there are no safety concerns regarding the application of study drug.

At Week 16, efficacy will be evaluated as the proportion of participants who achieve IGA-CHE-TS (the primary endpoint of the study). Additional efficacy assessments and patient-reported outcomes will be conducted as outlined in the SoA (see Table 3).

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

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. It is estimated that an individual will participate for approximately 40 weeks, including up to 28 days for screening, 16 weeks for DBVC study treatment, 16 weeks for OLE treatment, and up to 30 days for safety follow-up after the last application of study treatment.

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if they have completed all study visits, including the safety follow-up visit.

4.3. Study Termination

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

The sponsor may terminate the study electively if, for example, required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Age ≥ 18 years at the screening visit.
3. Diagnosis of CHE for at least 6 months prior to screening.

   Diagnosis of CHE is defined as HE lasting > 3 months or ≥ 2 recurrences within the previous 12 months.

   Note: Participants with hyperkeratotic, vesicular (eg, pompholyx), and fingertip eczema may be included.
4. Screening and baseline IGA-CHE score of 3 or 4.
5. Baseline CHE-related Itch NRS score ≥ 4. Baseline Itch NRS score is defined as the 7-day average of Itch NRS score directly before Day 1 (data from a minimum of 4 out of 7 days prior to Day 1 is needed).
6. Have been treated with at least 1 prescription CHE therapy or if such therapy was not advisable or contraindicated.
7. Willingness to avoid pregnancy or fathering children based on the criteria below.
   a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of ruxolitinib cream and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and negative urine pregnancy test before the first application on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last application of study ruxolitinib cream and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   c. Female participants not considered to be of childbearing potential as defined in Appendix A are eligible.

5.2. Exclusion Criteria

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

1. Known triggers for CHE (allergic or irritant, such as those identified by previous patch tests) cannot be avoided during the course of the study.
2. History of (within the past 5 years) or current AD or current psoriasis.

   Note: Participants with CHE due to AD are not eligible.
3. Concurrent conditions and history of other diseases:
   a. Other active skin disease or infection on the hands, including tinea manuum. In addition, foot eczema is excluded.
   b. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, or Wiskott-Aldrich syndrome).
   c. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
   d. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox, or impetigo) within 1 week before baseline.
   e. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton syndrome), pigmentation, or extensive scarring that in the opinion of the investigator may interfere with the evaluation of CHE lesions or compromise participant safety.
   f. Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or emergency department treatment within 3 months from baseline or stable asthma or COPD requiring budesonide more than 720 µg/day (2 puffs BID of 180-µg dose) or fluticasone more than 440 µg/day (2 puffs BID of 110-µg dose) or other equivalent high dose of other inhaled corticosteroids.
   g. Current or history of hepatitis B or C virus infection.
4. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
   a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction, or stroke within 6 months from Day 1 of study drug application, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mm Hg) unless approved by the medical monitor/sponsor.
   b. Participants with or a 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 venous thrombosis and pulmonary embolism.
   d. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.
   e. History of severe anemia, severe thrombocytopenia, or severe neutropenia.

5. Any of the following clinical laboratory test results at screening:
   a. Cytopenias, defined as follows:
      - Hemoglobin < 100 g/L (ie, 10 g/dL)
      - Absolute neutrophil count < 1.5×10^9/L (ie, 1500/µL)
      - Platelet count < 1×10^{11}/L (ie, 100,000/µL)
   b. Liver function tests:
      - AST or ALT ≥ 2.5 × ULN
      - Total bilirubin > 1.5 × ULN unless Gilbert syndrome
   c. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration 2021 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.
6. Use of any of the following treatments within the indicated washout period before the baseline visit:
   a. 12 weeks or 5 half-lives, whichever is longer – biologic agents (eg, dupilumab). For biologic agents with washout periods longer than 12 weeks (eg, rituximab), consult the medical monitor.
   b. 4 weeks – systemic corticosteroids or adrenocorticotropic hormone analogs; cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus); or oral alitretinoin or any other systemic treatment for CHE.
   c. 4 weeks for any topical or systemic JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib).
   d. 2 weeks or 5 half-lives, whichever is longer – strong systemic CYP3A4 inhibitors.
   e. 2 weeks – systemic antibiotics, immunizations with live-attenuated vaccines, or sedating antihistamines unless on a long-term stable regimen (nonsedating antihistamines are permitted).

      Note: Live-attenuated vaccines are not recommended during the DBVC period. COVID-19 vaccination is permitted.
   f. 1 week – use of any topical treatments for CHE (other than bland emollients, eg, Aveeno® creams, ointments, sprays, and soap substitutes), such as corticosteroids, calcineurin inhibitors, topical antipruritics (eg, doxepin cream), phosphodiesterase 4 inhibitors, coal tar (shampoo), topical antibiotics or antifungals, and 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.
7. Psoralen ultraviolet A or ultraviolet B therapy for CHE within 4 weeks before baseline.
8. Pregnant or lactating participants or those considering pregnancy during the period of their study participation.

9. History of alcoholism or drug addiction within 1 year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the administration schedule and study assessments.
10. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication or current enrollment in another investigational drug protocol.
11. Known allergy or reaction to any of the components of the study cream.
12. In the opinion of the investigator are unable or unlikely to comply with the administration schedule and study evaluations.
13. Committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.
14. Employees of the sponsor or investigator or otherwise dependents of them.

5.3. Lifestyle Considerations

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

If sunscreen or other cosmetics have been applied to the areas to be treated, participants should follow the guidance in Section 6.6 regarding concomitant medications.

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

Participants should not use hand sanitizer within 1 hour of study cream application. In addition, they should not wash or wet their hands or use hand sanitizer at a minimum within 1 hour after study cream application. In case of glove use, participants should ensure that the skin area where study cream is applied is completely dry before putting on glove(s).

5.4. Screen Failures

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

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

5.5. Replacement of Participants

No participants will be replaced at any time during this study. However, as noted in the COVID-19–related guidance (see Appendix B), due to the evolving situation of the COVID-19 pandemic, the sponsor may decide to recruit additional participants in the study beyond the expected number (eg, if a substantial number of participants withdraw early from the study).

6. STUDY TREATMENT

6.1. Study Treatment Administered

Ruxolitinib 1.5% cream or matching vehicle cream will be applied as a thin film BID, with applications at least 8 hours apart in the morning and in the evening at least 1 hour before bedtime.

On the first clinic visit day and subsequent in-house clinic visits, participants should not apply the study cream at home. The first application of the study cream on the day of the clinic visit will be done at the clinic.

At the baseline visit, an estimate of the %BSA to be treated (including hands and wrists [if applicable]) will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. The participant will apply a thin film of study cream in front of site staff at the baseline/Day 1 visit by applying study cream until all the affected areas to be treated are covered. All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 16) unless the participant meets criteria for stopping study cream. If there are new areas to be treated on the hands and wrists, including expansion of existing areas or development of new areas, after consultation with the investigator, study cream should be applied to these areas in addition to the areas treated at baseline, and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the IRT system to calculate the number of tubes of study cream to be dispensed.

During the OLE period starting at the Week 16 visit, CHE lesions will be evaluated by the investigator to confirm whether the participant still requires continuation of therapy (IGA-CHE score ≥ 1) or can otherwise (re)enter the observation/no treatment cycle (IGA-CHE score = 0). At Week 16, the IRT system will dispense a prespecified number of tubes according to the assessment of total BSA affected.

Between OLE study visits, participants will self-evaluate recurrence of CHE (if applicable) and will treat all areas identified with active changes. If all signs and symptoms of CHE resolve between study visits, participants will stop treatment applications 3 days after they have disappeared. If this 3-day window is during a study visit and the IGA score for CHE (if applicable) is 0, as assessed by the investigator, treatment is to be stopped at the study visit.

Participants will restart treatment of their CHE at the first sign of recurrence. In the event that new lesions are outside of the usual location and/or are more widespread than at baseline, the participant is required to contact the site for approval. Approval to treat additional areas may occur via telephone during the OLE period, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit.

All tubes (including caps) of study cream will be weighed before being dispensed. All returned tubes (including caps) of study cream will also be weighed.

Application instructions will be provided by the site staff, and the participant will record their daily applications via eDiary. Refer to the Study Pharmacy Manual for participant instructions for handling study cream.

Table 5 presents the study treatment information.

Table 5: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name:	Ruxolitinib	Vehicle
Mechanism of action:	JAK 1/2 inhibitor	Not applicable
Dosage formulation:	Cream	Cream
Treatment strength:	1.5%	Not applicable
Administration instructions:	DBVC period: Apply a thin film to affected areas identified at baseline in the morning and at least 1 hour before bedtime with applications at least 8 hours apart for 16 weeks. OLE period: Apply a thin film to affected areas in the morning and at least 1 hour before bedtime with applications at least 8 hours apart as needed for 16 weeks.	
Packaging and labeling:	Ruxolitinib or vehicle cream will be provided in 60-g tubes. Each tube will be labeled as required per country requirement.	
Storage:	15°C-30°C (59°F-86°F)	
Status of treatment in participating countries:	Investigational	

6.2. Preparation, Handling, and Accountability

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

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply study treatment. Participants should not wash their hands, if possible, within 1 hour after application of study cream. Refer to the Study Pharmacy Manual for participant instructions for handling of study cream.

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

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

- Delivery of study cream(s) to the study site.
- Inventory of study cream(s) at the site.

- Participant use of the study cream(s), including tube counts from each supply dispensed.
- Return of study cream(s) to the investigator or designee by participants.

The investigational product 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 cream. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used tubes of study cream until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee the destruction of any remaining study drug 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 investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study cream is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system. The IRT system will assign in a 1:1 ratio, stratified by baseline IGA-CHE score (3 or 4) and region (North America or outside of North America), the participant study number, track participant visits, randomize according to the defined parameters, maintain the blinding, and manage study cream inventory. Full details will be provided in the IRT Manual.

Participants, investigators, and the sponsor will be blinded to each participant's treatment assignment during the DBVC period. During the OLE period, participants and investigators will remain blinded to the treatment assignment during the DBVC period. Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.7 and refer to the IRT Manual).

6.4. Study Treatment Compliance

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

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

Drug accountability will be assessed by documenting the quantities of drug used between study visits (tube counts and weighing). At the first clinic visit and subsequent study visits, all tubes (including caps) of study cream will be weighed before being dispensed and when returned. Participants will be instructed to bring all study cream with them to the study visits in order for site staff to assess study cream accountability.

6.5. Dose Modifications

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

Temporary interruption could be due to an AE during the DBVC or OLE period (see Section 6.5.1) or clearance of the CHE during the OLE period, as described in Section 6.1.

6.5.2. Criteria for Permanent Discontinuation of Study Drug

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

- The occurrence of an AE that is related to the 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.
- Worsening of CHE that requires treatment with a prohibited concomitant medication.
- An AE that requires an interruption of study drug for more than 2 weeks.
- Confirmed Grade 4 laboratory abnormalities related to study drug (see Section 6.5.1).

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. All medications received up to 28 days before the first application of study treatment will be recorded in the eCRF. Any prior CHE treatments before the first application of study drug will be collected, including the reason for stopping the treatment (eg, inadequate response or intolerance). All medications received from the first application through 30 days after the last application of study treatment will be recorded in the eCRF. Any addition, deletion, or change in the dose/regimen of these medications will also be recorded.

Other relevant medications or procedures received more than 28 days before the first dose of study drug may be recorded in the eCRF at the discretion of the investigator or at the request of the sponsor based on emerging events during the study.

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

6.6.1. Permitted Medications and Procedures

The following are permitted during the study:

- Participants may use/continue to use bland emollients (eg, Aveeno® creams, ointments, sprays, or soap substitutes). Participants may not change or introduce a new emollient within 4 weeks of the baseline visit.
  - *Note:* Emollients should not be used 4 hours before and at least 1 hour after study cream application.
- If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide or titanium oxide based) with an SPF of at least 30 may be used not less than 4 hours before and at least 1 hour after study drug application.
- Participants may use nonsedating, over-the-counter antihistamines.
- Established treatment with sedating antihistamines (≥ 2 months prior to baseline) may be continued as long as no changes are made during the course of the study.
- Inhaled corticosteroids for bronchial asthma or COPD are allowed with the dose equivalent of budesonide (not to exceed 720 µg/day or 2 puffs BID of a 180-µg dose) or fluticasone (not to exceed 440 µg/day or 2 puffs BID of a 110-µg dose) or other equivalent inhaled corticosteroids.

6.6.2. Restricted Medications and Procedures

The use of the following medications and procedures is restricted to specified conditions:

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations) if deemed acceptable by the investigator from 7 days before the baseline visit through the follow-up visit.
- Use of any prescription medication to treat chronic medical conditions (such as hypertension) if on a stable regimen and if deemed acceptable by the investigator from 7 days before the baseline visit through the follow-up visit.
- Use of a short course of topical anti-infectives for an infection during the study (including antibacterial, antifungal, and antivirals) if used ≤ 5 days to treat skin infection. Anti-infective treatment should not be used for at least 4 hours before and 1 hour after application of study cream.
- Short-term use (< 5 days) of systemic corticosteroids may be permitted to treat acute AEs (eg, asthma) during the OLE period, and the decision to keep the participant in the study (or to permanently discontinue study cream) will be made in consultation with the medical monitor.

6.6.3. Prohibited Medications and Procedures

No rescue treatment or therapy is allowed during the study (see Section 6.5.2). In addition, the following are not permitted during the study:

- Any investigational medication other than the study drug.
- Treatment known to affect the course of CHE.
- Topical corticosteroids; topical calcineurin inhibitors; systemic corticosteroids (except short-term use of systemic corticosteroids to treat an AE during the OLE period, see Section 6.6.2); methotrexate, cyclosporin A, azathioprine and biological therapies, or other immunosuppressant agents; and oral alitretinoin or any other systemic treatment for CHE.
- Strong systemic CYP3A4 inhibitors.
- Phototherapy or tanning beds.
- Live-attenuated vaccination during the DBVC period.

  Note: COVID-19 vaccination is permitted.

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:

- Disease worsens requiring treatment with prohibited medication. The participant should be discontinued at the discretion of the investigator or based on discussions with the medical monitor.
- 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 disease progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, after 2 consecutive study visits and reinforcement of study drug application by site staff, a participant's drug usage exceeds one 60-g tube every 4 days; a participant who again fails to meet compliance benchmarks at a subsequent visit may be considered for withdrawal from the study. The medical monitor should be consulted for instruction on handling the participant.
- If, during the course of the study, a participant is found not to have met eligibility criteria, the 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 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 prior to the Week 16 or Week 32 visit, the ET visit should be conducted. Early termination will be referred to as ET1 if it occurs before Week 16 or ET2 if it occurs after Week 16 and before Week 32.

Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3. The date and time of the last application of study cream and the reason for discontinuation of study cream will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The ET visit should be performed and the date recorded.
- The status of the participant should be updated to ET in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), 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 a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

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(ies) in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study 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(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF and must be assigned a new participant ID number.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled/randomized in the study (Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood counts or physical examinations) and obtained before signing of the ICF may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days or less prior to Day 1). For participants who are randomized/enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

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

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the country's abbreviation, the site ID, and the participant ID number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit during both the DBVC period and the OLE period to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and/or eDiaries

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

Qualified clinical study staff will review the participants' eDiary entries for compliance. Participants who are noncompliant with their study drug schedule (defined as < 80% or > 120% of the expected number of applications between study visits) will have their administration

instructions reinforced by the investigator or a qualified designee, and the sponsor should be consulted by the investigator for instruction on the proper handling of participants who are not compliant during the DBVC period and the OLE period (see Section 6.4). Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the expected applications during participation in the DBVC period of the study.

Participants will be provided with a reminder card starting on Day 1 and at all DBVC and all OLE visits through Week 32. The reminder card will indicate the date and time of the next visit and will also remind the participant that their morning application of study cream (if applicable) will take place at the clinic under site supervision after blood draws and safety evaluations have been completed.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

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

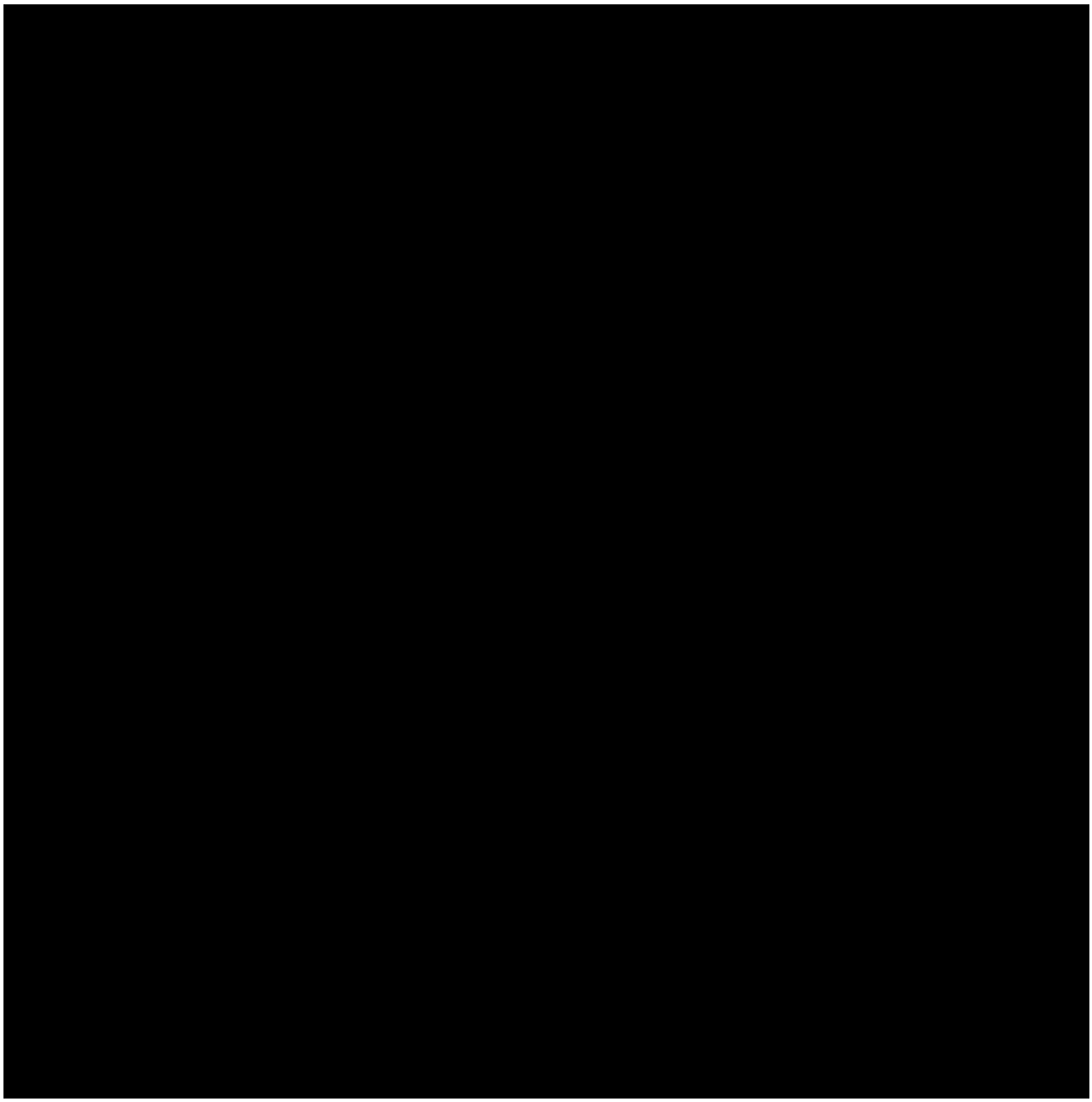
8.1.5.2. Disease Characteristics and Treatment History

Relevant medical and treatment history for CHE will be collected at screening by the investigator or qualified designee. Details regarding the participant's history of CHE, including date of diagnosis, relevant disease characteristics, prior treatments with outcome (eg, inadequate response or intolerance), and reason for stopping treatment will be recorded. Acceptable documentation includes a review of the participant's chart/medical records or investigator documentation based on communication with the participant's previous treating physician or the participant. A medical history of other conditions related to CHE will also be collected at this time.

8.2. Efficacy Assessments

8.2.1. Investigator's Global Assessment–Chronic Hand Eczema

The IGA-CHE is an overall severity rating on a scale from 0 to 4 as noted in [redacted] The IGA-CHE-TS is defined as an IGA-CHE score of 0 or 1 with ≥ 2-grade improvement from baseline and will be measured at the timepoints indicated in the SoA (see Table 3).



8.2.2. Hand Eczema Severity Index Score

The HECSI divides the hand into 5 areas for assessment (fingertips, fingers [except the tips], palms, back of hands, and wrists). Each of the 5 areas of the hand is assessed separately for erythema, induration/papulation, vesicles, fissuring, scaling, and edema using the following scale: 0, no skin changes; 1, mild disease; 2, moderate disease; and 3, severe disease. To determine the HECSI score, the affected area for each location (total of both hands) is given a score from 0 to 4 (0, 0%; 1, 1%-25%; 2, 26%-50%; 3, 51%-75%; and 4, 76%-100%) based on the extent of clinical symptoms. Finally, the score given for the extent at each location is multiplied by the total sum of the intensity of each clinical feature to calculate the HECSI score (range from 0 to a maximum severity score of 360 points; Held et al 2005). The HECSI score will be assessed at the timepoints indicated in the SoA (see Table 3).

8.2.4. Body Surface Area

Total %BSA affected (including hands and wrists [if applicable]) 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 Palmar Method as a guide (the palm plus 5 digits, with the fingers tucked together and the thumb tucked to the side [participant's handprint)] as 1% BSA and the thumb as 0.1% BSA).

8.2.5. Photography

Photographs of the hands and wrists (anterior and posterior) will be taken at visits indicated in Table 3 at all sites.

In addition, at select study sites that will collect skin samples (with tape discs), a note should be made in the medical record, and baseline photographs will be marked with the location of the target lesion and selected nonlesional area (see Section 8.2.3).

Ad hoc photography for skin-related AEs is recommended.

8.2.6. Patient-Reported Outcomes

Patient-reported outcomes will be assessed as outlined in the SoA (see Table 3).

8.2.6.1. eDiary Assessments

Participants will be issued a handheld device (eDiary) for daily assessments at the screening visit. The participant will be instructed to complete and record the CHE-related Itch NRS and Skin Pain NRS via an eDiary daily, in the evening beginning on the day of screening through Week 32 or ET.

Both the Itch NRS and Skin Pain NRS are a daily participant-reported measure (24-hour recall) of the worst level of itch or skin pain intensity related to CHE.

The participants will rate the following:

- CHE-related Itch NRS: Itch severity of their CHE by selecting a number from 0 (no itch) to 10 (worst imaginable itch) that best describes their worst level of itching in the past 24 hours.

- CHE-related Skin Pain NRS: Pain severity of their CHE by selecting a number from 0 (no pain) to 10 (worst imaginable pain) that best describes their worst level of pain in the past 24 hours.

The average of 7-day CHE-related Itch NRS prior to the baseline visit (minimum 4 out of 7 days' data required) will be used to determine if a participant meets the inclusion criteria.

Detailed directions for the administration of an eDiary will be provided in the Study Manual.

8.2.6.2. Dermatology Life Quality Index

The DLQI is a simple, 10-question validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days (Finlay and Khan 1994). The participant will answer the questionnaire as follows: 1) very much, 2) a lot, 3) a little, or 4) not at all.

8.2.6.3. Patient Global Impression of Change

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

The participant will be asked to select 1 response from the response options that best describe the overall change in their CHE since they started study treatment: 1) very much improved, 2) much improved, 3) minimally improved, 4) no change, 5) minimally worse, 6) much worse, and 7) very much worse.

8.2.6.4. Quality of Life in Hand Eczema Questionnaire

The QOLHEQ is a validated disease-specific instrument to assess disease-specific health-related quality of life in participants with CHE over the past 7 days (Ofenloch et al 2014). It consists of 30 items that are summarized according to impairments because of 4 domains: 1) symptoms, 2) emotions, 3) limitations in functioning, and 4) treatment and prevention. Each item is scored in a 5-point scale: 0) never, 1) rarely, 2) sometimes, 3) often, and 4) all the time.

8.2.7. Health Economics

8.2.7.1. EQ-5D-5L

Participants will complete the EQ-5D-5L questionnaire at the designated study visits. The EQ-5D-5L questionnaire is a standardized, validated instrument for use as a measure of health outcome (Herdman et al 2011). The EQ-5D-5L questionnaire will provide data for use in economic models and analyses, including developing health utilities or QALYs. The EQ-5D-5L questionnaire consists of the following 2 sections: the EQ-5D descriptive system and the EQ VAS.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: Level 1 = no problems, Level 2 = slight problems, Level 3 = moderate problems, Level 4 = severe problems, and Level 5 = extreme problems. This part of the EQ-5D-5L questionnaire provides a descriptive profile that can be used to generate a health state profile. For example, a participant in "health

state 12345" would have no problems with mobility, slight problems with self-care (washing or dressing), moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression. Each health state can potentially be assigned a summary index score based on societal preference weights for the health state. These weights, sometimes referred to as utilities, are often used to compute QALYs for use in health economic analyses. Health state index scores generally range from < 0 (where 0 is the value of a health state equivalent to dead; negative values represent values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility. The health state preferences often represent national or regional values and can therefore differ between countries/regions.

The EQ VAS records the participant's self-rated health on a vertical VAS (0-100), where the endpoints are labeled "the best health you can imagine" (100 score) and "the worst health you can imagine" (0 score).

8.2.7.2. Work Productivity and Activity Impairment Questionnaire v2.0 in Chronic Hand Dermatitis

The Work Productivity and Activity Impairment Questionnaire is a patient-reported quantitative assessment of the amount of absenteeism, presentism, and daily activity impairment attributable to a specific health problem. The WPAI-ChHD is a 6-item questionnaire used to assess the impact of chronic hand dermatitis (ChHD, the same as CHE in this context) on job performance and productivity in the past 7 days (Reilly et al 2003).

8.3. 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.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last application of study drug. Adverse events for enrolled participants that begin or worsen after informed consent 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 immediately, without undue delay and no later than within 24 hours (see Section 9.4). The investigator will submit any updated SAE data to the sponsor or designee immediately, without undue delay and no later than 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 AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

At the screening visit and the ET1 or ET2 visits, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. Fitzpatrick skin classification will be included as part of the physical examination at screening.

During the study, a targeted physical examination may be conducted by the investigator or medically qualified designee (per institutional policies and local standard of care) to assess AEs, symptoms/signs, laboratory abnormalities, or other findings. Findings from the targeted physical examination should be reported on the Adverse Events Form in the eCRF.

Height and body weight will be assessed at screening.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature and will be taken at the timepoints indicated in the SoA (see Table 3). Blood pressure and pulse will be taken with the participant in the sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment, 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.

8.3.4. Laboratory Assessments

See Table 8 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (eg, blood chemistries or hematology assessments) and will store the samples for PD analysis. Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and Table 3. Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly

abnormal during participation in the study or within 30 days after the last application of the study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significantly abnormal by the investigator or medical monitor.

It is not necessary to reassess chemistry or hematology at baseline (Day 1) if screening assessments were performed within 14 days of Day 1.

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

Table 8: Required Laboratory Analytes

Chemistry	Hematology	Serology	Pregnancy Testing
Albumin Alkaline phosphatase ALT AST Blood urea nitrogen or urea Creatinine Creatine kinase Glucose Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN)	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • Reticulocyte count • White blood cell count Differential count (absolute and %), including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	HIV	Human chorionic gonadotropin (WOCBP only) FSH (women of nonchildbearing potential only)

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

8.3.4.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening. Urine pregnancy tests will be performed locally, as outlined in the SoA (see Table 3), and as medically indicated (eg, in case of loss of menstrual cycle or 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 and continue participation in the study.

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

8.3.4.2. Serology

HIV screening assessment will be performed at the screening visit to rule out HIV infection. Generally, 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.

8.4. Pharmacokinetic Assessments

Pharmacokinetic parameters will not be evaluated in this study.

8.6. Unscheduled Visits

Unscheduled visits may occur at any time medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

8.7. End of Treatment and Early Termination

A participant who completes the Week 16 visit will have reached the end of double-blind treatment (EOT1) with study drug. A participant who completes the Week 32 visit will have reached the end of open-label treatment (EOT2) with study drug.

If a decision is made that the participant will permanently discontinue study drug prior to the Week 32 visit, then the ET visit should be conducted. Assessments for the ET visit will be the same as those for Week 32. Early termination will be referred to as ET1 if it occurs before Week 16 or ET2 if it occurs after Week 16 and before Week 32. 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 complete the ET procedures.

8.8. Follow-Up

The safety follow-up period is the interval between the Week 32 or ET visit and the scheduled follow-up visit, which should occur 30 days (+ 7 days' visit window) after the Week 32 or ET visit. All participants will have a safety follow-up visit 30 days (+ 7 days) following the end of treatment (Week 32/ET) to evaluate safety and disease control parameters. One exception to this would be for participants in the OLE period who have been in an observation/no treatment cycle with a total IGA-CHE score of 0 (clear) from Week 28 or earlier until Week 32; for such participants, the Week 32/ET visit will also count as the safety follow-up visit.

Adverse events and SAEs must be reported up until 1) 30 days after the last application of study drug or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

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

9.1. Definition of Adverse Event

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

9.2. Definition of Serious Adverse Event

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

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

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse 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 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 eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax 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) immediately, without undue delay but not later than within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

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

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 30 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Clinical Trials Regulation (EU) No. 536/2014 or per national regulatory requirements in participating countries.

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

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

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

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF.
- The investigator must report immediately, without undue delay but not later than within 24 hours of learning of its occurrence, any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form or Study Reference Manual for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Potential Drug-Induced Liver Injury

Not applicable.

9.6. Events of Clinical Interest

Not applicable.

9.6.1. Adverse Events of Special Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. The IRT system has an option to select for "Emergency Code Break" action for a given participant. After entering the study drug tube number and verification of the unmasking information, the investigator/subinvestigator will proceed to either final confirmation or cancellation of the code break procedure.

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

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

9.8. Pregnancy

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

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

Data on fetal outcome are collected for regulatory reporting and drug safety 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 the pregnancy of a study participant must be recorded and reported as described in Section 9.4.

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

9.9. Warnings and Precautions

Special warnings or precautions for the study 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 warnings or precautions in this study.

9.10. Product Complaints

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

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

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

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

9.11. Treatment of Overdose

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

10. STATISTICS

This section outlines the statistical analysis strategy and procedures for this study. If, after the study has begun, but before the final database lock, changes are made to primary and/or secondary analysis hypotheses or the statistical methods related to those hypotheses, the Protocol may be amended, consistent with ICH E9 (1998) and ICH E9 (R1) (2021). The detailed statistical analyses will be documented in the SAP.

10.1. Sample Size Determination

Approximately 180 participants will be randomized 1:1 to ruxolitinib 1.5% cream BID or vehicle cream BID.

The sample size is calculated to provide sufficient power (> 80%) to detect a difference between ruxolitinib 1.5% cream BID and vehicle cream BID for the primary and key secondary endpoints. The powers for different endpoints are provided in Table 9. The chi-square test with a 2-sided α of 0.05 is used to calculate the powers.

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

Table 9: Powering for Primary and Key Secondary Endpoints

Variables	Response Rates With Ruxolitinib 1.5% Cream BID	Response Rates With Vehicle Cream BID	Power
IGA-CHE-TS at Week 16	26%[ab]	10%[abc]	80%
ITCH4 at Week 16	40%[bc]	18%[bc]	90%
ITCH4 at Week 4	35%[bc]	12%[bc]	95%
ITCH4 on Day 7	30%[bc]	10%[bc]	92%

[a] Based on the results from a Phase 2b study of topical delgocitinib in CHE (Worm 2022).
[b] Based on the results from a Phase 3 study of topical delgocitinib in CHE (Bissonnette 2023).
[c] Based on the results from the 2 Phase 3 registrational AD studies, INCB 18424-303 and INCB 18424-304.

10.2. Populations for Analysis

Table 10 presents the populations for analysis.

Table 10: Populations for Analysis

Population	Description
ITT	The ITT population incudes all randomized participants.
Safety	The safety population includes all participants who applied study drug at least once. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
Open-label evaluable	The open-label evaluable population includes all participants who applied at least 1 dose of ruxolitinib cream during the OLE period.
PD evaluable	The PD evaluable population includes participants who applied study cream at least once and provided baseline PD sample and at least 1 postbaseline PD sample for analysis. The study translational scientist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

10.3. Level of Significance

The gatekeeping testing strategy for the primary and key secondary analyses will be implemented to control the overall Type I error rate, 2-sided $\alpha = 0.05$. These endpoints will be tested in a fixed sequence at 2-sided $\alpha = 0.05$ level in the following order:

- IGA-CHE-TS at Week 16
- ITCH4 response at Week 16
- ITCH4 response at Week 4
- ITCH4 response at Week 1 (Day 7)

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 and secondary endpoints.

10.4.1. Primary Analysis

The key parameters for the primary analysis are provided in Table 11. The primary analysis will be based on the ITT population. The primary alternative hypothesis (superiority of active ruxolitinib 1.5% cream BID compared with vehicle cream) will be tested at a 2-sided $\alpha = 0.05$ level using a Cochran-Mantel-Haenszel test stratified by IGA-CHE score (3 or 4) and region (North America or outside of North America). A summary of IGA-CHE-TS rates will be reported for each treatment group. The p-value and stratum-adjusted IGA-CHE-TS rate difference with 95% CI will be provided (Mantel and Haenszel 1959).

Table 11: Summary of Primary Analysis

Parameter	Definition
Treatment	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT population
Variable	IGA-CHE-TS at Week 16: defined as an IGA-CHE score of 0 or 1 with ≥ 2-grade improvement from baseline
Population-level summary	Stratum-adjusted IGA-CHE-TS rate difference with 95% CI

All nonresponders in the DBVC period, participants who discontinue study treatment at any time before the timepoint of interest, and participants who discontinue from the study for any reason will be defined as nonresponders for the nonresponder imputation analysis. Subgroup analysis by baseline characteristic (eg, IGA-CHE, region, or age) will be performed.

10.4.2. Key Secondary Objective

If the primary objective is achieved, the statistical hypotheses for the key secondary endpoint will be tested in the order specified in Section 10.3. Key secondary efficacy analysis at Week 16, Week 4, and Week 1 (Day 7) will be conducted in the ITT population. The statistical comparisons for binary outcomes (ITCH4) will be analyzed using a similar method as specified in the primary analysis. The stratum-adjusted ITCH4 rate difference (1.5% BID vs vehicle) and 95% CI will be computed in a similar way as in the primary analysis. A summary of analyses for the key secondary endpoints is provided in Table 12.

Table 12: Summary of Analyses for Key Secondary Endpoints

Parameter	Definition
Treatment	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT population
Variables	ITCH4 response at Week 16: Defined as a ≥ 4-point improvement in CHE-related Itch NRS score from baseline ITCH4 response at Week 4 ITCH4 response at Week 1 (Day 7)
Population-level summary	Stratum-adjusted IGA-CHE-TS rate difference with 95% CI

Note: Participants with missing observed data at the timepoint of interest, participants who discontinue study treatment at any time before the timepoint of interest, and participants who discontinue from the study for any reason will be defined as nonresponders. No rescue therapy or treatment switch is allowed in this study.

10.4.3. Secondary Analysis

All other secondary and exploratory efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. For the

time to achieve change from baseline in CHE-related Itch NRS score ≥ 4 and in CHE-related Skin Pain NRS score ≥ 2, a log-rank test stratified by randomization stratification factors will be used for comparisons between treatment groups. The hazard ratio and its 95% CI will be estimated based on the stratified Cox regression model using Efron's method accounting for ties. Kaplan-Meier curves will be presented by treatment groups. The number of participants, number of events, and number of censoring will be summarized by treatment groups. The Kaplan-Meier estimate of median time will be presented with its 95% CI. The 95% CI will be calculated using the method by Brookmeyer and Crowley (1982).

10.4.4. Safety Analyses

Safety analyses will be conducted for the safety population.

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first application of study 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 causal relationship to study drug will be considered treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

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

10.4.5. Analysis Plan

There are 2 formal planned analyses:

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

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

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

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

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

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

The investigator will be responsible for the following:

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

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

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

11.3. Data Quality Assurance

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

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

11.4. Data Privacy and Confidentiality of Study Records

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

data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

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

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte Corporation, 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
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

[b] If the male participant has a partner of childbearing potential the partner should also use contraceptives.

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

[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[e] Contraception methods that, in the context of this guidance, are considered to have low user dependency.

[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Number of Study Participants

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

Study Visits

Remote Site Visit Guidelines

In addition to the remote visits already specified in the Protocol, the evolving situation of the pandemic may require further travel restrictions and isolation requirements, or the investigator's benefit/risk assessment may determine it to be unsafe for participants to attend study visits at the investigational site. In such cases, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (telephone or video calls). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible, in addition to the mandatory on-site visits outlined below.
- No efficacy assessments can be performed via telemedicine (video call or phone call).
- Laboratory sampling: In order to support investigator oversight of participant safety and disease management, off-site laboratory sampling (in accordance with the SoA, see Table 3) may be allowed in 1 of 2 ways:
  - Use of home nursing services.
  - Instruction of the participant to undergo some laboratory tests at a local (nearby) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed at certified laboratories and copies of results provided to the site.

Mandatory On-Site Visits

The visits outlined below **must be performed in person** in order to capture the investigator's efficacy assessments and the patient-reported outcomes, even if the date that the participant eventually comes into the clinic deviates from the visit window.

No efficacy assessments can be performed via telemedicine (video call, telephone call, or photography).

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

During the placebo-controlled period, the following visits must be performed in person:

- Screening
- Day 1 (baseline)
- Week 4, 8, and 16 visits

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

- Week 32 visit

Investigational Medicinal Product Dispensing and Distribution

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

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

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

Clinical Trial Monitoring

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

If the study site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable

training. The study drug can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Other Considerations

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

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

Reimbursement of Extraordinary Expenses

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

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	19 APR 2023

Amendment 1 (19 APR 2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to increase the sample size and to remove the exit interview substudy. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 10.1, Sample Size Determination (Table 9: Powering for Primary and Key Secondary Endpoints)**

   Description of change: Increased sample size and updated the powering for endpoints.

   Rationale for change: Per recent results from a Phase 3 study of topical delgocitinib in CHE, the sample size was increased to detect the difference in response rates between ruxolitinib 1.5% cream and the vehicle cream.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities);** [redacted]

   Description of change: [redacted]

   Rationale for change: Per sponsor decision.

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

   Description of change: Removed photography from Week 2 and added to Week 4 visit.

   Rationale for change: Per sponsor decision.

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

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Approval Task	[redacted] Approver [redacted] 19-Apr-2023 21:39:52 GMT+0000
Approval Task	[redacted] Approver [redacted] 19-Apr-2023 22:30:22 GMT+0000
Approval Task	[redacted] Approver [redacted] 19-Apr-2023 23:26:22 GMT+0000
Approval Task	[redacted] Approver [redacted] 20-Apr-2023 12:37:11 GMT+0000
Approval Task	[redacted] Approver [redacted] 21-Apr-2023 14:57:56 GMT+0000

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