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: INCB 18424-226 Statistical Analysis Plan 29 MAY 2024

Statistical Analysis Plan

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

IND Number:	**77101**
EU CT Number:	**2022-502817-23-00**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
Protocol Version:	**INCB 18424-226 Protocol Amendment 1 dated 19 APR 2023**
CRF Approval Date:	**24 FEB 2024**
SAP Version:	**Original**
SAP Author:	[redacted] **Principal Biostatistician, Biostatistics**
Date of Plan:	**29 MAY 2024**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AD	atopic dermatitis
AE	adverse event
ASR	application site reaction
BID	twice daily
BMI	body mass index
BSA	body surface area
CHE	chronic hand eczema
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBVC	double-blind vehicle-controlled
DLQI	Dermatology Life Quality Index
eCRF	electronic Case Report Form
ET	early termination
HE	hand eczema
HECSI	Hand Eczema Severity Index
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
ITCH4	≥ 4-point improvement in ITCH score
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NCI	National Cancer Institute
NRS	numerical rating scale
OLE	open-label extension
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PT	preferred term
QOLHEQ	Quality of Life in Hand Eczema Questionnaire
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
VAS	visual analog scale
WPAI-ChHD	Work Productivity and Activity Impairment Questionnaire v2.0 in Chronic Hand Dermatitis

1. INTRODUCTION

This is a randomized, 16-week, double-blind, vehicle-controlled study with a 16-week open-label treatment extension period in participants with moderate to severe CHE with no history of (within the past 5 years) or current AD. Participants will be randomized 1:1 to ruxolitinib 1.5% cream BID or vehicle cream BID, with stratification by baseline IGA-CHE score and region. Participants will receive blinded study treatment (ruxolitinib 1.5% cream BID or vehicle) for 16 weeks (DBVC period). All participants continuing in the OLE period will receive ruxolitinib 1.5% cream BID and affected areas will be treated as needed until they clear.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the study Protocol. The Department of Biostatistics or designee will execute the scope of this plan.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 18424-226 Protocol Amendment 1 dated 19 APR 2023 and CRFs approved 24 FEB 2024. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: 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.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
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.
Exploratory	
[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.

3. STUDY DESIGN

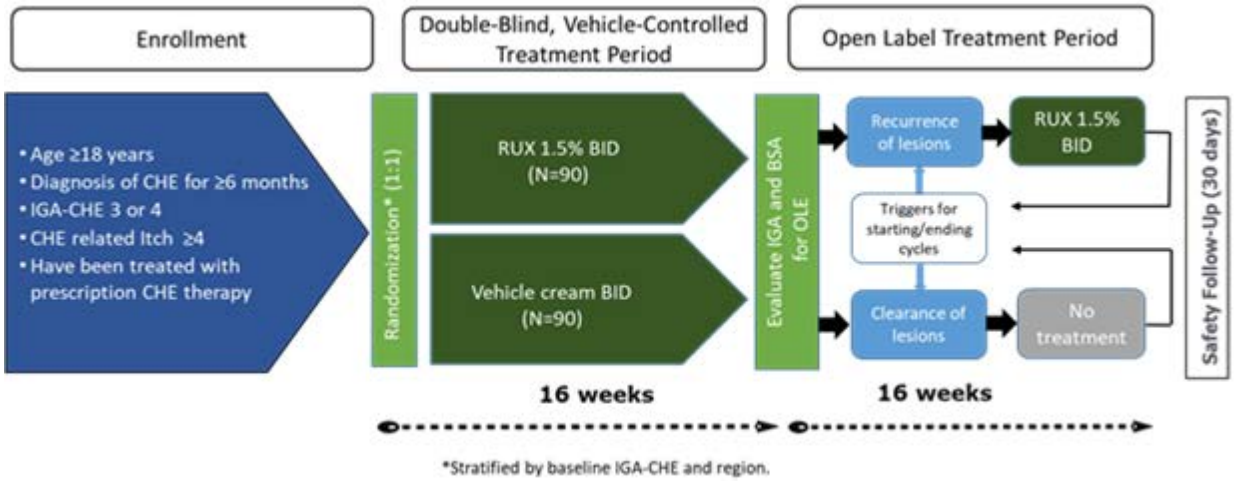
This is a Phase 2, randomized, double-blind, vehicle-controlled, 16-week study followed by a 16-week open-label treatment extension period. Approximately 180 participants with moderate to severe CHE with no history of (within the past 5 years) or current AD will be randomized 1:1 to either ruxolitinib 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.

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.

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.

Figure 1 presents the study design schema.

Figure 1: Study Design Schema



3.1. Randomization

In the DBVC period, participants will be randomized 1:1 either to ruxolitinib 1.5% cream BID or vehicle cream BID. Additionally, participants will be stratified by baseline IGA-CHE score (3 or 4) and region (North America or outside of North America).

3.2. Control of Type I Error

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)

3.3. Sample Size Considerations

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 2. 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 2: 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%[a,b]	10%[a,b,c]	80%
ITCH4 at Week 16	40%[b,c]	18%[b,c]	90%
ITCH4 at Week 4	35%[b,c]	12%[b,c]	95%
ITCH4 on Day 7	30%[b,c]	10%[b,c]	92%

[a] Based on the results from a Phase 2b study of topical delgocitinib in CHE (Worm et al 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.

3.4. Schedule of Assessments

Refer to INCB 18424-226 Protocol Amendment 1 dated 19 APR 2023 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first application of ruxolitinib cream or vehicle cream is administered to the participants.

For randomized participants not treated with any study drug, Day 1 is defined as the day of randomization.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before or on the day of first application of ruxolitinib cream or vehicle cream for DBVC period.

For randomized participants not treated with any study drug, baseline is defined as the last nonmissing assessment before or on the day of randomization for all parameters.

For participants who continue in the OLE period, baseline for OLE is defined as follows:

- For efficacy evaluation, baseline is the last nonmissing measurement obtained before or on the day of first application of study treatment in DBVC period.
- For safety evaluation, for participants who cross over from vehicle group to ruxolitinib cream, the baseline is the last nonmissing measurement obtained before or on the day of first application of ruxolitinib cream in the OLE period; for participants on ruxolitinib cream in both periods, baseline is the last nonmissing measurement obtained before or on the day of first application of study treatment in DBVC period.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first application is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first application and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first application and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Last Available Value

The last available value is the last nonmissing measurement obtained after starting ruxolitinib cream or vehicle cream and within 30 days after the last application of ruxolitinib cream or vehicle cream, or before the first application of ruxolitinib cream in the next period, whichever is earlier.

4.1.5. Handling of Missing and Incomplete Dates

Methods for handling missing dates are specified in relevant sections.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

Body mass index (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first application of study treatment.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first application of study treatment and is ongoing throughout the study or ends on/after the date of first application of study treatment.
- On/after the date of first application of study treatment and is ongoing or ends during the course of study treatment.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after the first application of study treatment. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, maximum, first quartile, third quartile, and 95% CI. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

5.2. Treatment Groups

This is a randomized, DBVC study followed by an OLE period. Data will be summarized based on treatment regimen that was assigned (ITT) or that the participant actually applied (safety).

For analyses in the ITT population and safety population, the treatment groups will be ruxolitinib 1.5% cream BID and vehicle cream BID.

For analyses in the open-label evaluable population, the treatment groups will be ruxolitinib 1.5% cream BID and vehicle cream BID to ruxolitinib 1.5% cream BID.

5.3. Analysis Populations

5.3.1. Intent-to-Treat Population

All participants who are randomized to the study will constitute the ITT population. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization regardless of the actual study treatment the participant might apply during their participation in the study.

The ITT population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.

5.3.2. Safety Population

All randomized participants who applied study treatment at least once will constitute the safety population. Treatment groups for this population will be determined according to the actual treatment the participant applied on Day 1 regardless of assigned study treatment.

All safety analyses in the DBVC period and throughout the study (from baseline to Week 32) will be conducted using the safety population.

5.3.3. Open-Label Evaluable Population

All participants who applied study treatment at least once during the OLE period will constitute the open-label evaluable population. All safety analyses for the OLE period will be conducted with the open-label evaluable population.

5.3.4. Pharmacodynamic-Evaluable Population

The PD evaluable population includes participants who applied study treatment 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.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics will be summarized for the ITT population during the DBVC period and open-label evaluable population in OLE period: age, age group, sex, race, ethnicity, weight, height, and BMI.

6.1.2. Baseline Disease Characteristics

Baseline disease characteristics summarized for the ITT population during the DBVC period include but are not limited to the following:

- Time since initial diagnosis of CHE
- Prior history of asthma (no/yes)
- Prior allergies (food, conjunctivitis, rhinitis) (no/yes)
- History of AD more than 5 years ago (no/yes)
- Type of CHE
- Diagnostic patch test result in the past 3 years (positive, negative, not available)
- CHE related to occupational factors (no/yes)
- Type of occupation if CHE related to occupational factor is yes
- History of skin infection on hands (including wrists) related to CHE requiring antibiotic treatment (no/yes)
- Time since onset of current CHE flare
- Number of CHE flares in the last 12 months
- Prior therapies for CHE received (no/yes)
- Contraindication to oral alitretinoin within the last 12 months (no/yes)
- Skin type using Fitzpatrick classification
- Total %BSA affected with CHE in current flare
- Baseline IGA-CHE score (3, 4)
- Baseline CHE-related Itch NRS score (by visit and daily)
- Baseline CHE-related Skin Pain NRS score (by visit and daily)

6.1.3. Prior Therapy for Chronic Hand Eczema

Prior therapies for CHE which include medication and other type of therapies will be coded using the WHO Drug Dictionary and summarized by treatment group. The type of treatment and reason for discontinuation will be summarized as well.

6.1.4. Medical History

For participants in the ITT Population during the DBVC period, medical history will be summarized and listed by assigned treatment groups. This summation will include the number and percentage of participants with medical history event for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participant

The number and percentage of participants who were randomized, treated, and completed the DBVC period and of participants who discontinued the treatment or withdrew from the study during the DBVC period with a primary reason for discontinuation will be summarized for ITT population during the DBVC period.

The number and percentage of participants who completed the OLE period and discontinued treatment or withdrew from the study during the OLE period with a primary reason for discontinuation will be summarized for the open-label evaluable population in the OLE period.

6.3. Protocol Deviations

Protocol deviations will be summarized by treatment groups in the DBVC and OLE periods, separately.

6.4. Exposure

For participants in the safety population during the DBVC period and open-label evaluable population in OLE period, descriptive statistics will be provided. That is, by treatment group for duration of treatment, average daily amount of cream applied (g), and total amount of cream applied (g). Duration of treatment with ruxolitinib cream or vehicle cream is defined as the number of days from Day 1 to the last record of ruxolitinib cream or vehicle cream application in the specific period.

6.5. Study Drug Compliance

Overall compliance (%) for the application of ruxolitinib cream or vehicle cream during the DBVC period will be calculated for all participants in the safety population as follows:

> overall application compliance (%) = 100 × [total number of nonmissing applications] / [total number of intended applications],

where the total number of nonmissing applications is the total number of applications that the participant actually applied during the study. The total number of intended applications is the number of planned applications minus the number of interrupted applications.

6.6. Prior and Concomitant Medication

For participants in the ITT population during the DBVC period, prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized as number and percentage of participants with prior and concomitant medications by WHO drug class and WHO drug term. For participants in the OLE period, only concomitant medications will be summarized.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. General Considerations

For all continuous variables, both the actual value and change and/or percentage from baseline (if available) will be analyzed.

All by-visit analyses will include the safety follow-up period if the data are available.

7.2. Efficacy Hypotheses

Not applicable.

7.3. Analysis of the Primary Efficacy Parameters

7.3.1. Primary Efficacy Measures

7.3.1.1. Investigator's Global Assessment–Chronic Hand Eczema

The IGA-CHE is an overall eczema severity rating on a 0 to 4 scale that will be assessed during site visits. The grades for the IGA-CHE are shown in Table 3.

Table 3: Investigator's Global Assessment-Chronic Hand Eczema

Grade	Severity	Features	Intensity
0	Clear	Erythema, scaling, hyperkeratosis/lichenification	Absent
		Vesiculation, edema, fissures	Absent
1	Almost clear	Erythema, scaling, hyperkeratosis/lichenification	At least 1 mild
		Vesiculation, edema, fissures	Absent
2	Mild	Erythema, scaling, hyperkeratosis/lichenification	At least 1 mild
		Vesiculation, edema, fissures	At least 1 mild
3	Moderate	Erythema, scaling, hyperkeratosis/lichenification	At least 1 mild or moderate
		Vesiculation, edema, fissures	At least 1 moderate
4	Severe	Erythema, scaling, hyperkeratosis/lichenification	At least 1 moderate or severe
		Vesiculation, edema, fissures	At least 1 severe

Source: Adapted from Ruzicka et al 2008.

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

7.3.2. Primary Efficacy Analyses

The key parameters for the primary analysis are provided in Table 4. The primary analysis will be based on the ITT population in the DBVC period. The primary alternative hypothesis (superiority of active ruxolitinib 1.5% cream BID compared with vehicle) will be tested at a 2-sided $\alpha = 0.05$ level using a CMH test stratified by stratification factors IGA-CHE score (3 or 4) and region (North America or outside of North America). The p-value and overall odds ratio

with 95% CI will be provided. Summary of IGA-CHE-TS rates will be reported for each treatment group. Stratum-adjusted IGA-CHE-TS rate difference (1.5% BID vs vehicle) and 95% CI will be computed using Mantel-Haenszel weights (Mantel and Haenszel 1959).

Table 4: 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 during the DBVC period, as well as all participants missing Week 16 assessment and who discontinue study treatment at any time before Week 16, or discontinue from the study for any reason, will be defined as nonresponders for the nonresponder imputation analysis.

7.3.3. Subgroup Analyses for Primary Endpoints

Subgroup analysis will be performed based on the following participant demographics and baseline disease characteristics variables for those participants whose data are available:

- Baseline IGA-CHE score (3, 4)
- Age (≥ 18 to 64, ≥ 65 years)
- Sex (male, female)
- Race
- Region (North America or outside of North America)

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Key Secondary Efficacy Measure

7.4.1.1. Chronic Hand Eczema-Related Itch Numerical Rating Scale Score

The CHE-related Itch NRS is a once-per-24 hours ("daily") patient-reported measure of the worst itch severity of their CHE assessed using an 11-point scale (0 = no itch to 10 = worst imaginable itch). Participants reported their worst itch severity in the evening beginning on the day of screening through Week 32 or ET.

The CHE-related Itch NRS score for baseline will be determined by averaging the 7 daily NRS scores before Day 1 (Day –7 to Day –1). The by-visit CHE-related Itch NRS score for postbaseline visits will be determined by averaging the 7 daily NRS scores before the visit day. If 4 or more daily scores are missing (out of the 7), the CHE-related Itch NRS score at the visit will be set to missing. For all daily itch related analyses including time to achieve Itch NRS score improvement of at least 2 or 4 points, baseline will be defined as the last available Itch NRS score during the last week prior to Day 1 (from Day −7 to Day −1).

The proportion of participants with a clinically relevant change in CHE-related itch (ITCH4), defined as a ≥ 4-point improvement in CHE-related Itch NRS score from baseline, will be summarized by treatment groups.

7.4.2. Key Secondary Efficacy Analysis

Key secondary efficacy analyses will be conducted in the ITT population in the DBVC period. If the primary objective is achieved, the statistical comparisons for key secondary endpoints will be tested with the procedures specified in Section 3.2. The same nonresponder imputation method as specified in the primary analysis will be used to handle missing Week 4 and Week 16 itch data.

For the key secondary endpoints of ITCH4 at Week 1 (Day 7), all participants who are missing Day 7 daily Itch NRS scores will be imputed using multiple imputation by fully conditional specification method. The variables to be included in the imputation regression model are treatment group, stratification factor, baseline itch score, and postbaseline daily itch score on Day 1 to Day 7. The corresponding binary response on Day 7 will be derived for each of the imputed datasets per the definition in Section 7.4.1.1.

The following sample SAS code will be used for the MI:

```
proc mi data=mi_wide seed=18424226 nimpute=30 out=impute_itch;
class trt01p strat1 strat2;
var trt01p strat1 strat2 base avald1 avald2 avald3 avald4 avald5
avald6 avald7;
fcs regpmm nbiter=30;
run;
```

All key secondary efficacy analyses will use stratified CMH test similar to the primary efficacy analysis. The summary of key secondary endpoints analysis is also provided in Table 5.

Table 5: 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 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 1: Participants with missing observed data at the timepoint of interest (Week 4, Week 16), participants who discontinue study treatment at any time before the timepoint of interest (Week 4, Week 16), and participants who discontinue from the study for any reason will be defined as nonresponders. Participants with missing observed data at Day 7 will be imputed using multiple imputation by fully conditional specification method. No rescue therapy or treatment switch is allowed in this study.
Note 2: ITCH4 is defined as a ≥ 4-point improvement in CHE-related Itch NRS score from baseline.

7.5. Analysis of Secondary Efficacy Parameters

7.5.1. Secondary Efficacy Measure

7.5.1.1. 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 are 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 total HECSI score, varying from 0 to a maximum severity score of 360 points (Held et al 2005).

The binary variable HECSI-75 will be equal to 1 for percentage improvement from baseline in HECSI-75 of ≥ 75% and will be equal to 0 for percentage improvement of < 75%. Hand Eczema Severity Index-90 is defined with the same pattern.

7.5.1.2. Chronic Hand Eczema-Related Skin Pain Numerical Rating Scale Score

The CHE-related Skin Pain NRS is a once-per-24 hours ("daily") patient-reported measure of the worst skin pain severity of their CHE assessed using an 11-point scale (0 = no pain to 10 = worst imaginable pain), in the evening beginning on the day of screening through Week 32 or ET.

The CHE-related Skin Pain NRS score for baseline will be determined by averaging the 7 daily NRS scores before Day 1 (Day –7 to Day –1). The by-visit CHE-related Skin Pain NRS score for postbaseline visits will be determined by averaging the 7 daily NRS scores before the visit day. If 4 or more daily scores are missing (out of the 7), the CHE-related Skin Pain NRS score at the visit will be set to missing. For all the daily pain-related analyses, baseline will be defined as the last available pain NRS score during the last week prior to Day 1 (from Day −7 to Day −1).

The proportion of participants with a clinically relevant change in CHE-related Skin Pain, defined as a ≥ 2-point improvement in CHE-related skin pain NRS score from baseline to Week 16, will be summarized by treatment groups.

7.5.1.3. Patient Global Impression of Change

The PGIC is a participants' 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 postbaseline 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. Missing values will not be imputed.

7.5.1.4. 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 in all the scheduled visits in both DBVC and OLE period (Finlay and Khan 1994).

The questionnaire is analyzed under 6 subscales as follows:

- Symptoms and feelings (Questions 1 and 2)
- Daily activities (Questions 3 and 4)
- Leisure (Questions 5 and 6)
- Work and school (Question 7)
- Personal relations (Questions 8 and 9)
- Treatment (Question 10)

The scoring of each question is as follows: Very much = 3; A lot = 2; A little = 1; Not at all = 0; Not relevant = 0; Question 7, "Prevented work or studying" Yes = 3.

The following imputation will be applied for incorrectly completed questionnaires:

- If 1 question is left unanswered, this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
- If 2 or more questions are left unanswered, the questionnaire is not scored.
- If question 7 is answered "yes," this is scored 3. If Question 7 is answered "no," but then either "a lot" or "a little" is ticked, this is then scored 2 or 1. If 'Not relevant" is ticked, the score for Question 7 is 0. If it is answered "no," but the second half is left incomplete, the score will remain 0.
- For the 6 subscales, if the answer to one question in a subscale is missing, that subscale should not be scored.

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

7.5.1.5. EQ-5D-5L

Participants will complete the EQ-5D-5L questionnaire at the scheduled visits in DBVC and OLE periods. 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 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.

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).

Missing values will not be imputed. The categorical outcomes for the 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) will be summarized. The change from baseline in EQ-5D VAS score will be analyzed.

7.5.1.6. Quality of Life in Hand Eczema Questionnaire

Participants will complete the QOLHEQ at the scheduled visits in DBVC and OLE periods. The QOLHEQ is a validated disease-specific instrument to assess disease-specific health-related quality of life in participants suffering from CHE over the past 7 days (Ofenloch et al 2014). It consists of 30 items that are summarized according to impairments for 4 subscales: 1) symptoms, 2) emotions, 3) limitations in functioning, and 4) treatment and prevention. Each item is scored in a scale of never, rarely, sometimes, often, all the time. The overall score is calculated by summing up all items.

Table 6 shows the scoring for each QOLHEQ item with the item number corresponds with the position of the item in the QOLHEQ.

Table 6: Scoring of Quality of Life in Hand Eczema Questionnaire

Item Number	Scoring of the item (never-rarely-sometimes-often-all the time)
Symptoms	
1	0 – 1 – 2 – 3 – 4
6	0 – 1 – 2 – 3 – 4
9	0 – 1 – 2 – 3 – 4
11	0 – 1 – 2 – 3 – 4
20	0 – 1 – 2 – 3 – 4
23	0 – 1 – 2 – 3 – 4
28[a]	0 – 1 – 1 – 2 – 3
Emotions	
5	0 – 1 – 2 – 3 – 4
8	0 – 1 – 2 – 3 – 4
10[a]	0 – 1 – 1 – 2 – 3
16	0 – 1 – 2 – 3 – 4
19	0 – 1 – 2 – 3 – 4
21	0 – 1 – 2 – 3 – 4
27	0 – 1 – 2 – 3 – 4
30	0 – 1 – 2 – 3 – 4

Table 6: Scoring of Quality of Life in Hand Eczema Questionnaire (Continued)

Item Number	Scoring of the item (never-rarely-sometimes-often-all the time)
Limitations in functioning	
2	0 – 1 – 2 – 3 – 4
3	0 – 1 – 2 – 3 – 4
12	0 – 1 – 2 – 3 – 4
14	0 – 1 – 2 – 3 – 4
15	0 – 1 – 2 – 3 – 4
17	0 – 1 – 2 – 3 – 4
25	0 – 1 – 2 – 3 – 4
29	0 – 1 – 2 – 3 – 4
Treatment and prevention	
4[a]	0 – 1 – 1 – 2 – 3
7	0 – 1 – 2 – 3 – 4
13	0 – 1 – 2 – 3 – 4
18	0 – 1 – 2 – 3 – 4
22	0 – 1 – 2 – 3 – 4
24	0 – 1 – 2 – 3 – 4
26	0 – 1 – 2 – 3 – 4

[a] In general, all items are scored 0-4 and only 3 items differ in their scoring structure.

The following imputation will be applied for incorrectly completed questionnaires (QOLHEQ 2024):

- If 1 question is left unanswered, this is scored as 0 and the subscale score is calculated by summing up all items.
- For the 4 subscales, if the answer to more than 1 question in a subscale is missing, that subscale should not be scored.
- If 4 or more questions are left unanswered, the overall score is set to missing and should not be scored.

7.5.1.7. Work Productivity and Activity Impairment Questionnaire Specific Health Problem v2.0 in Chronic Hand Eczema

Participants will complete the WPAI-ChHD questionnaire at the scheduled visits in DBVC and OLE periods. 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 (Reilly et al 1993). 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 last 7 days.

Work Productivity and Activity Impairment outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes, as follows:

Questions:

- 1 = currently employed
- 2 = hours missed due to CHE
- 3 = hours missed other reasons
- 4 = hours actually worked
- 5 = degree CHE affected productivity while working
- 6 = degree CHE affected regular activities

Scores:

Multiply below scores by 100 to express in percentages (%).

- Percent work time missed due to CHE: Q2 / (Q2 + Q4)
- Percent impairment while working due to CHE: Q5 / 10
- Percent overall work impairment due to CHE: [Q2 / (Q2 + Q4)] + ({1 – [Q2 / (Q2 + Q4)]} × [Q5 / 10])
- Percent activity impairment due to CHE: Q6 / 10

These impairment percentages will be summarized by visit and by treatment. Missing values will not be imputed.

7.5.2. Secondary Efficacy Analysis

All secondary efficacy analyses will be conducted based on the ITT population during the treatment period (DBVC and OLE periods).

7.5.2.1. Continuous Efficacy Endpoints

By-visit summary statistics for the following continuous measurements, including change from baseline and percentage change from baseline will be presented:

- CHE-related Itch NRS score
- CHE-related Skin Pain NRS score
- HECSI score
- DLQI total score
- EQ-5D-5L VAS score
- QOLHEQ total score
- WPAI-ChHD scores

The summary statistics includes sample size, mean, median, standard deviation, minimum, maximum, 1st quartile, 3rd quartile, and 95% CI will be presented by visits.

For PGIC score, summary statistics will be presented by treatment group at each postbaseline visit.

7.5.2.2. Categorical Efficacy Endpoints

For the following categorical parameters, summary statistics including sample size, frequency, and percentages will be presented by visits.

- Proportion of participants achieving an IGA-CHE-TS
- Proportion of participants achieving ≥ 2-point improvement in CHE-related Skin Pain NRS score up to Week 16 from baseline.
- Proportion of participants achieving ≥ 4-point improvement in CHE-related daily Itch NRS score from baseline to Day 14.

Statistical analysis for the ITCH4 response at Day 3 will be conducted using models similar to the key secondary endpoint of ITCH4 at Day 7, specified inSection 7.3.2.

For the following categorical endpoints, the number and percentage of participants will be summarized by treatment at each postbaseline visit:

- Proportion of participants in each category of EQ-5D-5L score
- Proportion of participants with each score on the PGIC

7.5.2.3. Time-To-Event Efficacy Endpoints

For the time to achieve CHE-related Itch NRS score improvement of at least 4 points and time to achieve CHE-related Skin Pain NRS score improvement of at least 2 points, a log-rank test stratified by randomization stratification factors will be used for between treatment group comparisons. The hazard ratio and its 95% CI will be estimated based on the stratified Cox regression model using Efron's method accounting for ties. Kaplan-Meier curves will be presented by treatment 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).

7.6. Analysis of Exploratory Efficacy Parameters

7.6.1. Exploratory Efficacy Analysis

CCI

8. PHARMACODYNAMICS

8.1. Pharmacodynamic Analyses

Pharmacodynamic parameters will be summarized descriptively.

9. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

9.1. General Considerations

The analyses in this section will be provided for the safety population in the DBVC and open-label evaluable population in the OLE period. Cumulative TEAEs across the treatment periods (DBVC and OLE periods) will be summarized. Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first application of study drug and within 30 days of the last application of study drug. For participants who crossover treatments, the first application date is period-specific, and the end date is 30 days after the last application date in this period, or the first application date in the next period, whichever comes first. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug application.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0 (Grade 1 to 5). The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

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

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Application site reactions are AEs that occur at the site of drug application. A summary of ASRs will be provided.

9.2.2. Adverse Event Summaries

An overall summary of AEs by treatment period will include:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants who had any ASRs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any treatment-related TEAEs
- Number (%) of participants who temporarily interrupted study drug in any of the treated areas because of TEAEs
- Number (%) of participants who permanently discontinued study drug because of TEAEs
- Number (%) of participants who had a fatal TEAE

The following summaries will be produced by MedDRA term (if 2 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of ASRs by MedDRA PT in decreasing order of frequency
- Summary of Grade 3 or higher AEs by SOC and PT
- Summary of Grade 3 or higher AEs by PT in decreasing order of frequency
- Summary of serious TEAEs by SOC and PT
- Summary of serious TEAEs by PT in decreasing order of frequency
- Summary of treatment-related TEAEs by SOC and PT
- Summary of treatment-related TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or higher treatment-related TEAEs by SOC and PT
- Summary of treatment-related serious TEAEs by SOC and PT
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of study drug by SOC and PT

Adverse events of interest will be summarized in the following categories:

- Cytopenias
  - Anemia
  - Thrombocytopenia
  - Neutropenia
- Herpes zoster
- Nonmelanoma skin neoplasms
- Liver function test elevations
- Malignancies
- Major Adverse Cardiovascular Events
- Venous and arterial thromboembolic events
- Thrombocytosis and elevated mean platelet volume

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

All laboratory assessments will be performed using a central laboratory except for urine pregnancy tests (as applicable). Laboratory values and change from baseline values will be summarized descriptively by visit, and non-numeric test values will be tabulated when necessary.

The baseline value will be determined using the last nonmissing value collected before the first study drug application, prioritizing scheduled assessments for baseline identification over unscheduled visits. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

9.3.2. Laboratory Value Summaries

Clinical laboratory tests, including hematology and serum chemistry, will be performed at the Protocol-specified visits. If specific safety issues arise, additional unscheduled laboratory tests/analyses may be performed at the discretion of the investigator.

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple laboratory nonmissing values for a participant's particular test within a visit window, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never

low), and both low and high will be calculated for each test. This shift summary will be produced for each test for the safety population in the DBVC period, as well as the open-label evaluable population in the OLE period. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline as well. The denominator for the percentage calculation will use the number of participants in the baseline category.

9.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiratory rate will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 7. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change from baseline greater than 25%. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 7: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 155 mmHg	≥ 85 mmHg
Diastolic blood pressure	≤ 100 mmHg	≥ 40 mmHg
Pulse	≤ 100 bpm	≥ 45 bpm
Temperature	≤ 38°C	≥ 35.5°C
Respiratory rate	≤ 24 breaths/min	≥ 8 breaths/min

10. INTERIM ANALYSES

No formal interim analysis is planned for this study. 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.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 8.

Table 8: Statistical Analysis Plan Versions

SAP Version	Date
Original	29 MAY 2024

11.1. Changes to Protocol-Defined Analyses

Not applicable.

11.2. Changes to the Statistical Analysis Plan

Not applicable.

12. REFERENCES

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APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristic		
1.1 Disposition		
1.1.1	Analysis Populations	All
1.1.2.1	Summary of Participant Disposition in the DBVC Period	ITT
1.1.2.2	Summary of Participant Disposition in the OLE Period	Open-Label Evaluable
1.1.3	Summary of Number of Participants Enrolled by Country and Site	ITT
1.1.4.1	Summary of Protocol Deviations in the DBVC Period	ITT
1.1.4.2	Summary of Protocol Deviations in the OLE Period	Open-Label Evaluable
1.2 Demography and Baseline Characteristics		
1.2	Summary of Demographics and Baseline Characteristics	ITT
1.3 Baseline Disease Characteristics		
1.3	Summary of Baseline Disease Characteristics	ITT
1.4 Prior Medication and Concomitant Medication		
1.4.1	Summary of Prior Medications	ITT
1.4.2	Summary of Prior Therapies for CHE	ITT
1.4.3.1	Summary of Concomitant Medications in the DBVC Period	ITT
1.4.3.2	Summary of Concomitant Medications in the OLE Period	Open-Label Evaluable
1.5+ Others		
1.5	Summary of General Medical History	ITT
Efficacy		
2.1 IGA-CHE-TS		
2.1.1	Summary and Analysis of Participants Achieving IGA-CHE-TS in the Treatment Period	ITT
2.1.2	Summary and Analysis of Participants Achieving IGA-CHE-TS in the Treatment Period With Nonresponder Imputation	ITT
2.1.3	Summary and Analysis of Participants Achieving IGA-CHE-TS by Baseline IGA-CHE Score in the Treatment Period	ITT
2.1.4	Summary and Analysis of Participants Achieving IGA-CHE-TS by Age Group in the Treatment Period	ITT
2.1.5	Summary and Analysis of Participants Achieving IGA-CHE-TS by Sex in the Treatment Period	ITT
2.1.6	Summary and Analysis of Participants Achieving IGA-CHE-TS by Race in the Treatment Period	ITT
2.1.7	Summary and Analysis of Participants Achieving IGA-CHE-TS by Region in the Treatment Period	ITT

Table No.	Title	Population
2.2 CHE-Related Itch NRS Score		
2.2.1	Summary and Analysis of Participants Achieving ≥ 4-Point Improvement in CHE-Related Itch NRS Score in the Treatment Period by Visit	ITT
2.2.2	Summary and Analysis of Participants Achieving ≥ 4-Point Improvement in CHE-Related Itch NRS Score in the Treatment Period with Nonresponder Imputation by Visit	ITT
2.2.3	Summary and Analysis of By-Visit CHE-Related Itch NRS Score in the Treatment Period	ITT
2.2.4	Summary and Analysis of Time to ≥ 4-Point Improvement in CHE-Related Itch NRS Score in the Treatment Period	ITT
2.2.5	Summary and Analysis of Daily CHE-Related Itch NRS Score	ITT
2.2.6	Summary and Analysis of Participants Achieving ≥ 4-Point Improvement in CHE-Related Itch NRS Score From Day 1 to Day 7	ITT
2.3 CHE-Related Skin Pain NRS Score		
2.3.1	Summary of Participants Achieving ≥ 2-Point Improvement in CHE-Related Skin Pain NRS Score in the Treatment Period	ITT
2.3.2	Summary of By-Visit CHE-Related Skin Pain NRS Score in the Treatment Period	ITT
2.3.3	Summary of Time to ≥ 2-Point Improvement in CHE-Related Skin Pain NRS Score in the Treatment Period	ITT
2.4 HECSI		
2.4.1	Summary of By-Visit HECSI Score in the Treatment Period	ITT
2.4.2	Summary of Participants Achieving HECIS-75 in the Treatment Period	ITT
2.4.3	Summary of Participants Achieving HECIS-90 in the Treatment Period	ITT
2.5 PGIC		
2.5.1	Summary of By-Visit PGIC Score in the Treatment Period	ITT
2.5.3	Summary of Participants Achieving a PGIC Score of 1 or 2 in the Treatment Period	ITT
2.6 DLQI		
2.6.1	Summary of Total DLQI Total Score in the Treatment Period	ITT
2.7 EQ-5D-5L		
2.7.1	Summary of EQ-5D VAS Score in the Treatment Period	ITT
2.7.2	Summary of Participants in Each Category of EQ-5D Score in the Treatment Period	ITT
2.8 QOLHEQ		
2.8.1	Summary of QOLHEQ Total Score in the Treatment Period	ITT
2.9 WPAI-ChHD		
2.9.1	Summary of WPAI-ChHD Score in the Treatment Period	ITT
Safety		
3.1 Exposure		
3.1.1.1	Summary of Exposure in the DBVC Period	Safety
3.1.1.2	Summary of Exposure in the OLE Period	Open-Label Evaluable
3.1.1.3	Summary of Exposure From Baseline to Week 32	Safety
3.1.2	Summary of Study Drug Compliance in the DBVC Period	Safety

Table No.	Title	Population
3.2 Adverse Events		
3.2.1.1.1	Overall Summary of Treatment-Emergent Adverse Events in the DBVC Period	Safety
3.2.1.1.2	Overall Summary of Treatment-Emergent Adverse Events in OLE Period	Open-Label Evaluable
3.2.1.1.3	Overall Summary of Treatment-Emergent Adverse Events for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.2.1.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.2.1.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.2.1.3	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.2.1.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term From Baseline to Week 32	Safety
3.2.3.1.1	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the DBVC Period	Safety
3.2.3.1.2	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the OLE Period	Open-Label Evaluable
3.2.3.1.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.3.1.4	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency From Baseline to Week 32	Safety
3.2.3.3.1	Summary of Application Site Reactions by MedDRA Preferred Term in Decreasing Order of Frequency in the DBVC Period	Safety
3.2.3.3.2	Summary of Application Site Reactions by MedDRA Preferred Term in Decreasing Order of Frequency in the OLE Period	Open-Label Evaluable
3.2.3.3.3	Summary of Application Site Reactions by MedDRA Preferred Term in Decreasing Order of Frequency for Participants who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.3.3.4	Summary of Application Site Reactions by MedDRA Preferred Term in Decreasing Order of Frequency From Baseline to Week 32	Safety
3.2.4.1.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.4.1.2	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in OLE Period	Open-Label Evaluable
3.2.4.1.3	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.5.1.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the DBVC Period	Safety
3.2.5.1.2	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the OLE Period	Open-Label Evaluable
3.2.5.1.3	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.6.1.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in DBVC Period	Safety

Table No.	Title	Population
3.2.6.1.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.6.1.3	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.7.1.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the DBVC Period	Safety
3.2.7.1.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the OLE Period	Open-Label Evaluable
3.2.7.1.3	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.8.1.1	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in DBVC Period	Safety
3.2.8.1.2	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.8.1.3	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.9.1.1	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in DBVC Period	Safety
3.2.9.1.2	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the OLE Period	Open-Label Evaluable
3.2.9.1.3	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.10.1.1	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in DBVC Period	Safety
3.2.10.1.2	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.10.1.3	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.11.1.1	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.11.1.2	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.11.1.3	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.12.1.1	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.12.1.2	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.12.1.3	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety

Table No.	Title	Population
3.2.13.1.1	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption in any of the Treated Areas by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.13.1.2	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption in any of the Treated Areas by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.13.1.3	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption in any of the Treated Areas by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.14.1.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.14.1.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.14.1.3	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term for Participants who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.15.1.1	Summary of Treatment-Emergent Adverse Events of Interest by MedDRA System Organ Class and Preferred Term in the DBVC Period	Safety
3.2.15.1.2	Summary of Treatment-Emergent Adverse Events of Interest by MedDRA System Organ Class and Preferred Term in the OLE Period	Open-Label Evaluable
3.2.15.1.3	Summary of Treatment-Emergent Adverse Events of Interest by MedDRA System Organ Class and Preferred Term for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
3.2.16.1.1	Summary of Treatment-Emergent Adverse Events of Interest by MedDRA Preferred Term in Decreasing Order of Frequency in the DBVC Period	Safety
3.2.16.1.2	Summary of Treatment-Emergent Adverse Events of Interest by MedDRA Preferred Term in Decreasing Order of Frequency in the OLE Period	Open-Label Evaluable
3.2.16.1.3	Summary of Treatment-Emergent Adverse Events of Interest by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Applied Ruxolitinib Cream Throughout the Study (Baseline to Week 32)	Safety
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3.3.1	Summary of Laboratory Values – Hematology in the DBVC Period	Safety
3.3.1.2	Summary of Laboratory Values – Hematology in the OLE Period	Open-Label Evaluable
3.3.2.1	Summary of Laboratory Values – Chemistry in the DBVC Period	Safety
3.3.2.2	Summary of Laboratory Values – Chemistry in the OLE Period	Open-Label Evaluable
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTCAE Grade – to the Worst Abnormal Value in the DBVC Period	Safety
3.3.3.2	Shift Summary of Hematology Laboratory Values in CTCAE Grade – to the Worst Abnormal Value in the OLE Period	Open-Label Evaluable
3.3.4.1	Shift Summary of Chemistry Laboratory Values in CTCAE Grade – to the Worst Abnormal Value in the DBVC Period	Safety
3.3.4.2	Shift Summary of Chemistry Laboratory Values in CTCAE Grade – to the Worst Abnormal Value in the OLE Period	Open-Label Evaluable

Table No.	Title	Population
3.3.5.1	Shift Summary of Hematology Values – to the Worst Abnormal Value in the DBVC Period	Safety
3.3.5.2	Shift Summary of Hematology Values – to the Worst Abnormal Value in the OLE Period	Open-Label Evaluable
3.3.6.1	Shift Summary of Chemistry Values – to the Worst Abnormal Value in the DBVC Period	Safety
3.3.6.2	Shift Summary of Chemistry Values – to the Worst Abnormal Value in the OLE Period	Open-Label Evaluable
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3.4.2.1	Summary of Diastolic Blood Pressure in the DBVC Period	Safety
3.4.2.2	Summary of Diastolic Blood Pressure in the OLE Period	Open-Label Evaluable
3.4.3.1	Summary of Pulse in the DBVC Period	Safety
3.4.3.2	Summary of Pulse in the OLE Period	Open-Label Evaluable
3.4.4.1	Summary of Respiratory Rate in the DBVC Period	Safety
3.4.4.2	Summary of Respiratory Rate in the OLE Period	Open-Label Evaluable
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Figures

Figure No.	Title	Population
4.1 IGA-CHE-TS		
4.1.1.1	Proportion of Participants Achieving IGA-CHE-TS in the Treatment Period	ITT
4.1.1.2	Proportion of Participants Achieving IGA-CHE-TS in the DBVC Period With Nonresponder Imputation	ITT
4.1.2.1	Proportion of Participants Achieving IGA-CHE-TS By Baseline IGA-CHE Score in the Treatment Period	ITT
4.1.2.2	Proportion of Participants Achieving IGA-CHE-TS by Age Group in the Treatment Period	ITT
4.1.2.3	Proportion of Participants Achieving IGA-CHE-TS by Sex in the Treatment Period	ITT
4.1.2.4	Proportion of Participants Achieving IGA-CHE-TS by Race in the Treatment Period	ITT
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4.1.3	Forest Plot of Response Rate Difference in Achieving IGA-CHE-TS at Week 16	ITT

Figure No.	Title	Population
CHE-Related Itch NRS Score		
4.3.1.1	Proportion of Participants Achieving ≥ 4-point Improvement in CHE-Related Itch NRS Score in the Treatment Period	ITT
4.3.1.2	Proportion of Participants Achieving ≥ 4-point Improvement in CHE-Related Itch NRS Score in the DBVC Period With Nonresponder Imputation	ITT
4.3.2.1	Mean and Standard Error Plot of CHE-Related Itch NRS Score by Visit in the Treatment Period	ITT
4.3.2.2	Mean and Standard Error Plot of Change From Baseline in CHE-Related Itch NRS Score by Visit in the Treatment Period	ITT
4.3.3.1	Proportion of Participants Achieving ≥ 4-point Improvement in CHE-Related Daily Itch NRS Score from Day 1 to Day 14	ITT
4.3.3.2	Proportion of Participants Achieving ≥ 4-point Improvement in CHE-Related Daily Itch NRS Score from Day 1 to Day 7 using Multiple Imputation	ITT
4.3.4.1	Mean and Standard Error Plot of CHE-Related Daily Itch NRS Score in the Treatment Period	ITT
4.3.4.2	Mean and Standard Error Plot of Change From Baseline in CHE-Related Daily Itch NRS Score in the Treatment Period	ITT
4.3.5.1	Kaplan-Meier Curve of the Time to ≥ 4-Point Improvement in Itch NRS Score in the DBVC Period	ITT
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4.4.1	Proportion of Participants Achieving ≥ 2-point Improvement in CHE-Related Skin Pain NRS Score in the Treatment Period	ITT
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4.4.2.2	Mean and Standard Error Plot of Change From Baseline in CHE-Related Skin Pain NRS Score by Visit in the Treatment Period	ITT
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4.6.1	Proportion of Participants Achieving HECSI-75 in the Treatment Period	ITT
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4.7.1	Mean and Standard Error Plot of PGIC Score by Visit in the Treatment Period	ITT
4.7.2	Proportion of Participants Achieving a PGIC Score of Either 1 or 2 in the Treatment Period	ITT
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4.8.1	Mean and Standard Error Plot of DLQI Total Score in the Treatment Period	ITT
4.8.2	Mean and Standard Error Plot of Change From Baseline in DLQI Total Score in the Treatment Period	ITT
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4.9.1	Mean and Standard Error Plot of EQ-5D-5L VAS Score in the Treatment Period	ITT
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Figure No.	Title	Population
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4.10.1	Mean and Standard Error Plot of QOLHEQ Total Score in the Treatment Period	ITT
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4.12.1	Mean and Standard Error Plot of WPAI-ChHD Score in the Treatment Period	ITT
4.12.2	Mean and Standard Error Plot of Change From Baseline in WPAI-ChHD Score in the Treatment Period	ITT
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4.13.1.3	Box Plot of Percentage Change From Baseline in Hemoglobin (g/L) by Visit in the DBVC Period	Safety
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4.13.2.3	Box Plot of Percentage Change From Baseline in Platelets (10^9/L) by Visit in the DBVC Period	Safety
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4.13.3.2	Box Plot of Change From Baseline in Neutrophils (10^9/L) by Visit in the DBVC Period	Safety
4.13.3.3	Box Plot of Percentage Change From Baseline in Neutrophils (10^9/L) by Visit in the DBVC Period	Safety
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4.13.4.3	Box Plot of Percentage Change From Baseline in Leukocytes (10^9/L) by Visit in the DBVC Period	Safety
4.13.5.1	Box Plot of Lymphocytes (10^9/L) by Visit in the Treatment Period	Safety
4.13.5.2	Box Plot of Change From Baseline in Lymphocytes (10^9/L) by Visit in the DBVC Period	Safety
4.13.5.3	Box Plot of Percentage Change From Baseline in Lymphocytes (10^9/L) by Visit in the DBVC Period	Safety
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4.13.7.1	Box Plot of Reticulocytes (10^9/L) by Visit in the Treatment Period	Safety
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Listings

Listing No.	Title
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2.2	Protocol Deviations
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Listing No.	Title
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