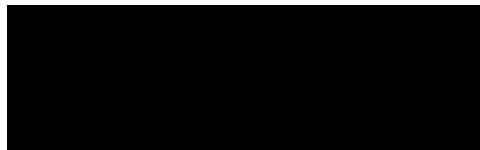


Official Title: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)

NCT Number: NCT04839380

Document Date: Statistical Analysis Plan Version Final: 17-Jun-2022



Statistical Analysis Plan

Study Title: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)

Protocol Number and Version: INCB 18424-901 Amendment 3 dated 09-MAY-2022

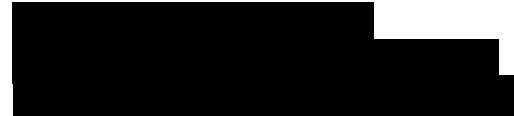
Product: Ruxolitinib cream

Sponsor: Incyte Corporation
1801 Augustine Cut-Off,
Wilmington, Delaware, USA 19803

Date: 17-Jun-2022

Version: Final v1.0

Prepared by:



	STATISTICAL ANALYSIS PLAN, Version Final v1.0
Protocol Number: INCB 18424-901	Sponsor: Incyte Corporation
Study Title: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)	

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	Version Date	Author	Summary of Changes
Final v1.0	17-Jun-2022	[REDACTED]	Initial version

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Study Title: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)	

SIGNATURE PAGE

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[REDACTED]	[REDACTED]	cyte Corporation	05-oct-2022 22:45:23 EDT
[REDACTED]	[REDACTED]		05-oct-2022 16:12:38 EDT

This statistical analysis plan will be reviewed and revised as needed. The most recent version will replace the previous version in place.

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ABBREVIATIONS

AD	Atopic Dermatitis
AE	adverse event
ATC	anatomical therapeutic chemical
BID	twice daily
BSA	body surface area
CI	confidence interval
COVID-19	Coronavirus disease 2019
CRF	case report form
CRO	contract research organization
EASI	Eczema Area and Severity Index
eCRF	electronic case report form
ET	early termination
IGA	Investigator Global Assessment
IGA-TS	Investigator Global Assessment-Treatment Success (IGA score of 0 or 1 with \geq 2-grade improvement from baseline)
ITT	intent-to-treat (population)
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
mPP-NRS	modified peak pruritus numerical rating scale (current itch intensity)
NRS	numerical rating scale
PP-NRS	peak pruritus numerical rating scale (24-hour recall period)
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System®
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TLF	tables, listings, and figures
TSQM-9	Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication
WHO-DD	World Health Organization Drug Dictionary

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Incyte Corporation clinical protocol INCB 18424-901. The analyses described in the SAP are based upon the protocol version Amendment 3 dated 09-MAY-2022.

This SAP has been developed prior to database lock and final analyses. All final analyses will be performed after the clinical trial data are entered into the database, any discrepancies in the data are resolved, the lock of the database, and following the signature of the SAP.

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2 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the efficacy of ruxolitinib 1.5% cream on pruritus in participants with atopic dermatitis (AD).	<p>Primary efficacy endpoint:</p> <ul style="list-style-type: none"> Change from baseline in Peak-Pruritus Numerical Rating Scale (PP-NRS) at Day 2 (24-hour recall period after first application).
Secondary	
To evaluate the efficacy of ruxolitinib 1.5% cream in participants with AD.	<p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> Change from baseline in Modified Peak-Pruritus Numerical Rating Scale (mPP-NRS) (current itch intensity) at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 3 through Day 29. Proportion of participants achieving at least a 1-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 2 through Day 29. Proportion of participants achieving at least a 2-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 2 through Day 29. Time to minimal clinically important difference (MCID) (≥ 2-grade reduction in PP-NRS and mPP-NRS from baseline).

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OBJECTIVES	ENDPOINTS
	<ul style="list-style-type: none"> • Change from baseline in Investigator's Global Assessment (IGA) at Day 8, Day 15, and Day 29. • Proportion of participants achieving the Investigator's Global Assessment-Treatment Success (IGA-TS) (score of 0 or 1 in IGA with at least a 2-grade reduction from baseline) at Day 8, Day 15, and Day 29.
To evaluate the local and systemic safety and tolerability of ruxolitinib 1.5% cream in participants with AD.	<p>Secondary safety/efficacy endpoints:</p> <ul style="list-style-type: none"> • Incidence and severity of local and systemic adverse events (AEs).
Exploratory	

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3 STUDY DESIGN

3.1 Overall Design

This is a Phase 2, open-label, single-arm study evaluating the effect of ruxolitinib 1.5% cream on itch. This study will include approximately 48 adult participants (18-65 years old, inclusively) who have at least a 6-month history of AD and at least a 3-month history of chronic itch.

All participants will read and sign an Informed Consent Form (ICF) prior to any study procedures being performed and then undergo screening for study eligibility. Participants who meet initial screening requirements will be given access to an eDiary to complete the PP-NRS each morning (24-hour recall period), from screening to Day -1 and from Day 2 to the Day 29 visit. Participants must be willing and able to complete the eDiary on a daily basis for the duration of the study. During the last 7 days prior to Day 1 (run-in period; Day -7 to Day -1), participants will be required to complete at least 4 of 7 PP-NRS assessments in their eDiary. Inclusion of participants completing fewer than 4 of 7 PP-NRS questionnaires during the last 7 days of the screening period (run-in period) must be approved by the sponsor.

After a screening period of no more than 37 days (from Day -37 to Day -1, including a 7-day run-in period), participants who fulfill all of the inclusion criteria, none of the exclusion criteria, and have a baseline mean PP-NRS score ≥ 4.0 during the run-in period will be eligible to start the treatment period. The baseline mean PP-NRS score is defined as the average of all nonmissing PP-NRS scores reported during the run-in period.

During the treatment period, participants will have topical treatment with ruxolitinib 1.5% cream applied BID as a thin film for 28 (± 2) days (last application on the evening prior to the Day 29 visit). The study drug will be applied on all AD lesions, with a maximum treated area $\leq 20\%$ BSA. All original areas of involvement on Day 1 (even in the event of lesions clearing), and any new lesions (a maximum of $\leq 20\%$ BSA can be treated) must be treated until the evening prior to the Day 29 visit. On Day 1, participants will remain at the study center until after the 6-hour mPP-NRS assessment (approximately an 8-hour stay at the site). The 12-hour mPP-NRS assessment will be done at home just prior to the evening study drug application. On Day 8 and Day 15, the morning application of the study drug will be at the study center under the supervision of study staff. Other study drug applications will be self-administered by the participants at home. The study schema is shown in Figure 1 in the protocol.

Study drug application will occur in the morning and evening from Day 1 until the day prior to the Day 29 visit, with approximately 12 hours between applications. The evening dose should be applied at least 1 hour before bedtime. On Day 1, the mPP-NRS assessments should occur as close as possible to the scheduled time relative to the first study drug application. In addition, the 12-hour mPP-NRS should be completed before the evening study drug application. On Day 2, the PP-NRS assessment should be completed approximately 24 hours after the first study drug application and before the Day 2 morning dose. Refer to Table 5 for the sequence and timing of

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these assessments and allowed windows on Day 1 and Day 2. From Day 3 until the Day 29 visit, the PP-NRS should be completed once daily, at approximately the same time in the morning, and prior to the study drug application.

Efficacy will be evaluated using the PP-NRS (worst itch over a 24-hour period), the mPP-NRS (current itch at the time of assessment), and the 5-point IGA.

The Body Surface Area (BSA) and Eczema Area and Severity Index (EASI) will be used to evaluate the participant's AD severity on Day 1 and will be characterized during the study.

Medical photographs of the target lesion(s) and application site adverse events (AEs) will be taken during the study. Participants will be asked to complete the Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM-9) at the end of the treatment period (or ET, if applicable).

Safety will be assessed by collecting AEs, performing comprehensive and targeted physical examinations, and evaluating clinical laboratory assessments.

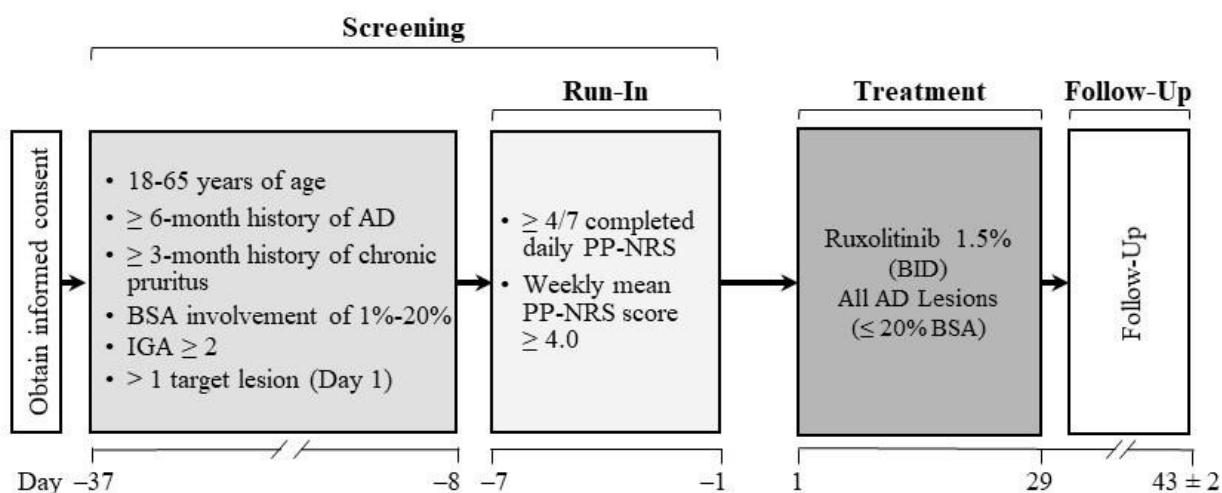


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3.2 Schedule of Events

Table 3 of the protocol provides a description of the procedures planned at each visit.

Figure 1: Study Design Schema



3.3 Treatment

The treatment group is: ruxolitinib 1.5%, BID for 28 days.

3.4 Randomization, Replacement, and Unblinding Procedures

This is an open-label, single-arm study. No participants will be replaced at any time during this study.

3.5 Changes to the Analysis from the Protocol

No changes were made from the planned analysis in protocol.

4 POPULATIONS FOR ANALYSIS

4.1 Enrolled Analysis Set

The Enrolled analysis set will include all participants who sign the ICF.

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4.2 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all enrolled participants who complete the run-in period (ie, not be a screen failed) and meet the inclusion and exclusion criteria. The ITT analysis set will be used for the summary of demographics, baseline characteristics, and participants disposition.

4.3 Modified Intent-to-Treat Analysis Set

The modified Intent-to-Treat (mITT) analysis set is a subset of the ITT analysis set, including participants who have both baseline and at least 1 post-baseline PP-NRS or mPP-NRS assessment within the treatment period. The mITT analysis set will be used for all efficacy analyses.

4.4 Per Protocol Analysis Set

The per protocol analysis set is a subset of the mITT analysis set, excluding participants with major protocol deviations that could potentially affect the efficacy evaluations. The per protocol analysis set will be used as supportive information for all efficacy analyses.

4.5 Safety Analysis Set

The Safety analysis set will include all enrolled participants who received at least 1 application of ruxolitinib 1.5% cream. All safety analyses will be conducted using the safety analysis set.

5 GENERAL CONSIDERATIONS

Formats and layouts of tables, listings, and figures (TLF) will be provided in a separate document (output general layout is described in [Appendix 1](#)).

5.1 Sample Size

Approximately 36 participants were planned to be enrolled into the study to receive ruxolitinib 1.5% cream. The sample size calculation was based on the CI for 1-sample mean. With an approximate 10% missing assessment rate at 24 hours, a sample size of 36 is required to produce a 2-sided 95% CI for the expected change from baseline in PP-NRS (24-hour recall period), with a precision of 0.57. The SD of 1.64 is estimated from 2 Phase 3, double-blind, randomized studies (INCB 18424-303 and INCB 18424-304). To ensure data quality and support study interpretation after deviations from protocol related to the timing of efficacy assessments were observed in the first participants enrolled, it was decided to enroll an additional 12 participants for a total of approximately 48 participants to be included.

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5.2 Baseline

Unless otherwise specified, baseline value will be defined as the last non-missing assessment before or on Day 1 and prior to the first application of study drug (including unscheduled assessments). If the last non-missing assessment is performed on the same date as the first study treatment and time or timepoint is not available, the assessment will be considered as baseline, except for adverse events (AEs) and medications starting on the first study treatment dose date which will be considered post-baseline.

For PP-NRS, the baseline is defined as the average of all non-missing PP-NRS scores reported during the 7-day run-in period (Day -7 to Day -1).

5.3 Reference Start Date and Analysis Day

Analysis Day will be calculated from the first study treatment date and will be used to show start/end day of assessments or events.

Analysis day = (Date of event – Date of first dose administration) + 1 if date of event is on or after the date of first dose administration of study treatment;
 = (Date of event – Date of first dose administration) if date of event is before the date of first dose administration of study treatment.

In the situation where the assessment/event date is partial or missing, Analysis Day will be missing.

5.4 Windowing Conventions

No windowing conventions apply for this study.

5.5 Descriptive Statistics

All continuous variables will be summarized by presenting the number of participants, mean, standard deviation, standard error of the mean, median, minimum and maximum. Categorical variables will be presented as frequencies and percentages. Summary tables will be presented by visit, when applicable.

Change from baseline will be calculated as:

Assessment value at post-baseline visit X – Baseline value.

Percent change from baseline (%) will be calculated as:

(Assessment value at postbaseline visit X – Baseline value) / Baseline value * 100.

Percent change from baseline will be missing in situation where Baseline value equals to 0.

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5.6 Statistical Tests

No formal statistical comparisons will be performed. Confidence intervals (CIs) will be two-sided with 95% coverage. Unless otherwise specified, confidence intervals for proportions will be calculated using the Clopper-Pearson method, as applicable.

5.7 Handling of Retests, Unscheduled Visits, and Early Termination Data

When retests measurements are done, the retest measurement will be considered for the summary analysis. All data from retest visits will be listed.

Unscheduled measurements will not be summarized in by-visit summary tables or figures. However, they will be included in shift summary tables. All data from unscheduled visits will be listed.

Early Termination visit assessments will be summarized as a separate visit in by-visit outputs. All data from early termination visits will be listed.

5.8 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

6 STATISTICAL CONSIDERATIONS

6.1 Adjustments for Covariates

Not applicable.

6.2 Handling of Dropouts or Missing data

No imputation will be made for efficacy data. See [Appendix 2](#) for handling of completely or partially missing dates for prior and concomitant medications and adverse events.

6.3 Interim Analysis and Data Monitoring

No formal interim analysis is planned for this study.

6.4 Multicenter Studies

Not applicable.

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6.5 Multiple Comparisons/Multiplicity

No adjustments for multiple comparison will be made for this study.

6.6 Examination of Subgroups

No subgroup analysis is planned for this study.

7 STUDY PARTICIPANTS

7.1 Disposition of Participants

All participants who provide informed consent will be accounted for in this study. The number of participants screened, rescreened, and who failed screening (screen failures) will be presented. The reason for screen failure will be presented for all screened participants who failed screening and rescreening, if applicable. The percentage of participants screen failures will be calculated using the number of participants screened as denominator. The percentage of reasons for screen failure will be calculated using the number of screen failures as denominator. The number of participants enrolled (who provide informed consent) and included in each analysis set will be presented and percentages will be based on the number of enrolled participants.

End of treatment status and treatment discontinuation related to COVID-19 or not will be presented. The percentage of end of treatment status will be calculated using the number of participants in the ITT analysis set. The percentage of treatment discontinuation related to COVID-19 or not will be calculated using the number of participants in the ITT analysis set who did not complete the treatment. Study completion status and the reason for study discontinuation will also be presented, including discontinuation related to COVID-19. The percentage of reasons for study discontinuation will be calculated using the number of participants in the ITT analysis set who did not complete study as denominator (and related or not to COVID-19, if applicable). Otherwise, the percentages will be calculated using the number of participants included in the ITT analysis set as denominator.

Number of days in the study will be calculated as follows and summarized:

$$\text{Number of days in study} = \text{Date of completion/discontinuation} - 1^{\text{st}} \text{ dose date} + 1.$$

If a participant had no dose, the number of days in the study will be left as missing. A listing of participants' disposition and a listing of participants included in each of the analysis sets will also be provided based on the Enrolled analysis set. Information on first screening for participants who were rescreened, including the rescreened participant identifier, will be presented under the first screening participant identifier.

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7.2 Protocol Deviations

Protocol deviations will be classified as major or minor prior to database lock.

The number of participants with at least one major protocol deviation will be summarized by deviation category on the safety analysis set. Important protocol deviations will be summarized in a similar way. A listing of all protocol deviations will also be provided.

The number of events and the number and percentage of participants with at least one protocol deviation associated with COVID-19 will be summarized by deviation category using the safety analysis set. A listing of all protocol deviations associated with COVID-19 will also be provided.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized with descriptive statistics based on the ITT analysis set and on the per protocol analysis set. The list of demographics and baseline characteristics to be summarized will include:

- Age (years) – as recorded in the CRF
- Sex at birth
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Race* (White, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific islander, Black or African American, Unknown)
- Baseline Height (cm)
- Baseline Weight (kg)
- Fitzpatrick skin type
- Baseline Body Surface Area for eligibility (%) (excluding palms, soles, scalp, genitals, and folds)
- Baseline Total Body Surface Area affected (%)
- Baseline Body Surface Area treated (%)
- Baseline Peak-Pruritus Numerical Rating Scale (run-in period mean score)
- Baseline Modified Peak-Pruritus Numerical Rating Scale

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- Baseline Investigator Global Assessment
- Baseline Eczema Area and Severity Index
- Baseline Transepidermal Water Loss (TEWL) (lesional and non-lesional)

*Participants who reported more than one race will be summarized as 'Multiple' race in the table. All races selected will be displayed in the listing.

A listing of all demographics and baseline characteristics will be provided for the ITT analysis set.

9 SURGICAL AND MEDICAL HISTORY

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0.

General surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) on the safety analysis set. A participant who experienced the same surgical and medical history event multiple times will be counted only once for the corresponding PT. Similarly, if a participant experienced multiple surgical and medical history events within the same SOC, the participant will be counted only once for that SOC. Surgical and medical history events will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

A listing of all general surgical and medical history events will be provided.

Disease-targeted Atopic Dermatitis (AD) medical history will be summarized based on the safety analysis set. Disease duration, chronic itch (yes/no), prior history of asthma (yes/no), prior allergies (yes/no), history of contact dermatitis (yes/no), common complications associated, time from onset, presence of head and neck, facial and periorbital involvement (yes/no), and the number of AD episodes/flare-ups over the last 12 months will be reported.

The disease duration (in years) will be calculated as follow:

Disease duration = (Date of first dose of study treatment – Date of initial AD diagnostic)/365.25.

The time from onset (in years) will be calculated as follow:

Time from onset = (Date of first dose of study treatment – Current date of onset of AD episode)/365.25.

Completely or partially missing dates for the date of AD diagnostic and the current date of onset of AD will be imputed as follow:

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- Completely missing: Leave missing.
- Missing day and month: Impute to January 1st.
- Missing day: Impute to the 1st of the month.

A listing of all disease-specific AD history, including date of AD diagnostic and date of current onset, will be provided.

10 PRIOR AND CONCOMITANT MEDICATIONS AND THERAPIES

10.1 Prior and Concomitant Medications

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD), B3 March 2021.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dose. Concomitant medications are defined as any medication taken after the first study treatment dose, including those who started prior to the first study treatment date and continued past that date. See [Appendix 2](#) for handling of completely or partially missing dates for prior and concomitant medications.

Incidence of prior and concomitant medications will be tabulated separately by ATC level 3 and PT on the safety analysis set. A participant with the same medication taken multiple times will be counted only once for the corresponding PT. Similarly, if a participant has taken more than one medication within the same ATC level, then the participant will be counted only once for that ATC. A listing of all prior and concomitant medications will be provided.

All disease-specific (AD) prior medications and therapies will be tabulated separately in a similar way and based on the safety analysis set. Additionally, a listing of all prior medications and therapies related to AD will be provided.

10.2 Non-drug Therapies and Surgical Procedures

Non-drug therapies and surgical procedures will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0.

Prior non-drug therapies and surgical procedures are defined as any non-drug therapy and surgical procedure started and discontinued prior to the first study treatment dose. Concomitant non-drug therapies and surgical procedures are defined as any non-drug therapy and surgical procedure taken after the first study treatment dose, including those who started prior to the first study treatment date and continued past that date. See [Appendix 2](#) for handling of completely or partially missing dates for non-drug therapies and surgical procedures.

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Incidence of prior and concomitant non-drug therapies and surgical procedures will be tabulated separately by system organ class (SOC) and preferred term (PT) on the safety analysis set. A participant who experienced the same non-drug therapies and surgical procedures event multiple times will be counted only once for the corresponding PT. Similarly, if a participant experienced multiple non-drug therapies and surgical procedures events within the same SOC, the participant will be counted only once for that SOC. Non-drug therapies and surgical procedures will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

A listing of all non-drug therapies and surgical procedures will be provided.

11 STUDY TREATMENT EXPOSURE AND TREATMENT COMPLIANCE

Duration of exposure to study treatment, in days, will be computed as follows:

$$\text{Duration of exposure} = [(\text{Date of last dose of study treatment} - \text{Date of first dose of study treatment}) + 1]$$

Compliance with study treatment (%) will be calculated as follows:

$$\frac{\text{Number of applications per participant eDiary}}{\text{Total number of intended applications}} \times 100$$

For each participant, the total number of intended applications corresponds to 2 applications per day from the day of first dose until the end of treatment date:

$$\text{Total number of intended applications} = [(\text{Date of end of treatment} - \text{Date of first dose of study treatment}) + 1] \times 2.$$

Descriptive statistics for the duration of exposure, number of applications (based on the participant's eDiary) and compliance to study treatment will be presented based on the safety analysis set. Frequency distribution will also be presented for the following compliance categories: <80% , 80% to 120%, >120%.

A summary of cumulative dose applied will be presented based on the safety analysis set. Cumulative dose will be derived based on the information on the dispensed tubes weight and returned tubes weight captured in the drug accountability form. Cumulative dose (in grams) will be computed as follow:

$$(\text{Sum of tubes weight dispensed} - \text{Sum of tubes weight returned}).$$

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If the information on tube weight is missing (i.e. tube not returned), cumulative dose will be missing.

A listing of exposure, compliance, study treatment administrations, treatment interruptions and study treatment accountability will be provided.

12 EFFICACY ANALYSIS

Unless otherwise noted, all efficacy analysis will be performed on the mITT analysis set. The per protocol analysis set will be used as supportive information for all efficacy analyses.

12.1 Primary Endpoint

12.1.1 Peak-Pruritus Numerical Rating Scale

The intensity of pruritus (itch) will be recorded daily in the eDiary from the screening visit until Day -1 and from Day 2 to the Day 29 visit, using the Peak-Pruritus Numerical Rating Scale (PP-NRS) (24-hour recall period). This NRS will be evaluated by asking participants to assign a numerical score representing their itch at the worst moment during the previous 24 hours on a scale of 0 to 10, with 0 being no itch and 10 being the worst itch imaginable.

The PP-NRS will be analyzed as follow:

- Change from baseline in PP-NRS at Day 2 (24-hour recall period after first application).

12.1.2 Primary Analysis

The primary endpoint, change in PP-NRS from baseline at Day 2 (24-hour recall period after first application), will be analyzed descriptively. The 95% CI will be provided for the mean change.

12.2 Secondary Endpoints

12.2.1 Modified Peak-Pruritus Numerical Rating Scale

On Day 1 only, participants will be asked to evaluate the current intensity of their itch at the time of assessment (ie, prior to the morning study drug application and 15, 30 minutes, 1, 2, 4, 6, and 12 hours after the morning study drug application; the 12-hour evaluation will occur prior to the second daily study drug application) on a scale from 0 to 10, with 0 indicating no itch and 10 indicating the worst imaginable itch. The modified Peak-Pruritus Numerical Rating Scale (mPP-NRS) (current itch intensity) was modified from the PP-NRS.

The mPP-NRS will be analyzed as follow:

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- Change from baseline in mPP-NRS (current itch intensity) at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1.
- Proportion of participants achieving at least a 1-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1.
- Proportion of participants achieving at least a 2-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1.

12.2.2 Peak-Pruritus Numerical Rating Scale

The PP-NRS is defined in section 12.1.1. The PP-NRS will be analyzed as follow:

- Change from baseline in PP-NRS from Day 3 through Day 29.
- Proportion of participants achieving at least a 1-grade decrease from baseline in PP-NRS from Day 2 through Day 29.
- Proportion of participants achieving at least a 2-grade decrease from baseline in PP-NRS from Day 2 through Day 29.

12.2.3 Minimal Clinically Important Difference

The minimal clinically important difference (MCID) corresponds to an achievement of ≥ 2 -grade reduction in PP-NRS and mPP-NRS from baseline.

The MCID will be analyzed as follow:

- Time to MCID for PP-NRS (≥ 2 -grade reduction in PP-NRS from baseline).
- Time to MCID for mPP-NRS (≥ 2 -grade reduction in mPP-NRS from baseline).

The time to MCID will be defined as the time from the date (time) of first dose to the date (time) of first occurrence of MCID. The time to MCID for the PP-NRS will be reported in days, and the time to MCID for the mPP-NRS will be reported in hours.

12.2.4 Investigator's Global Assessment

The Investigator's Global Assessment (IGA) of the current state of the disease is a 5-point morphological assessment of overall disease severity.

The IGA will be analyzed as follow:

- Change from baseline in IGA at Day 8, Day 15, and Day 29.

The Investigator's Global Assessment-Treatment Success (IGA-TS) is defined as an IGA score of 0 or 1 with at least a 2-grade reduction from baseline. The IGA-TS will be analyzed as follow:

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- Proportion of participants achieving the IGA-TS (score of 0 or 1 in IGA with at least a 2-grade reduction from baseline) at Day 8, Day 15, and Day 29.

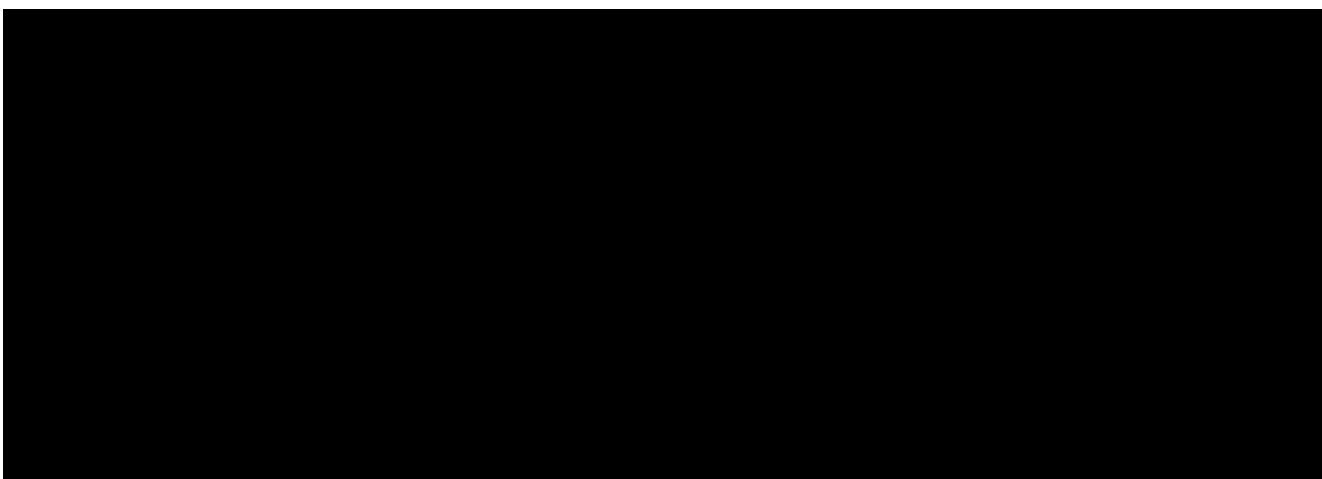
12.2.5 Secondary Endpoints Analysis

Descriptive statistics will be presented for all secondary efficacy endpoints, by visit and timepoint (if applicable). The change from baseline and percent change from baseline in PP-NRS, mPP-NRS and IGA, and proportion endpoints for PP-NRS, mPP-NRS, and IGA-TS, will be analyzed descriptively at each visit. The 95% CI will be provided for the mean change, percent change and the proportions (using the Clopper-Pearson method). For proportion endpoints, percentages will be based on the number of participants with a response at the specified visit and timepoint.

The proportion of participants achieving an IGA score of 0 or 1 and associated 95% CI (using the Clopper-Pearson method) will also be reported descriptively.

The time to MCID will be analyzed using Kaplan Meier estimation for PP-NRS and mPP-NRS. A participant will be considered censored if he has not met the event of interest at the end of the study or if the participant is lost to follow up at last observation. Those participants will be censored at their last available mPP-NRS or PP-NRS assessment date or time. Survival curves will also be presented.

A line graph presenting the value and a line graph presenting the change from baseline in mPP-NRS over time will be produced. The value and change from baseline in PP-NRS over time and value and change from baseline in IGA will be presented similarly.



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12.4 Other Analyses

12.4.1 Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication

The Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a 9-item measure that assesses the most common dimensions participants use to evaluate their medication (ie, global satisfaction, effectiveness, and convenience). The results for each scale (global satisfaction, effectiveness, and convenience) are presented from 0 to 100, where higher scores represent better satisfaction. Scoring method for each scale is presented in [Appendix 3](#).

TSQM-9 data for each scale will be summarized separately by visit using descriptive statistics. All TSQM-9 data will be listed.

12.4.2 Transepidermal Water Loss

Transepidermal water loss (TEWL) quantifies the clinical severity of AD and the associated effect on skin barrier function. Three TEWL readings are taken at each location (lesional and non-lesional), and the median will be calculated for these three readings. If the participant performs less than 3 readings, the median will still be calculated based on available readings. Descriptive statistics for the median of the three TEWL measurements will be presented by location and visit,

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and the corresponding change from baseline when appropriate. The 95% CI will be provided for the mean change from baseline. All Transepidermal Water Loss measurements will be listed.

12.4.3 Eczema Area and Severity Index

The Eczema Area and Severity Index (EASI) is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration (papules), excoriation, and lichenification (each scored from 0 to 3 separately) for each of 4 body regions, with adjustment for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. Scoring method for the Eczema Area and Severity Index is presented in [Appendix 4](#).

Descriptive statistics for the EASI will be presented by visit, and the corresponding change and percent change from baseline when appropriate. The 95% CI will be provided for the mean change and percent change.

Additionally, the proportion of participants with at least a 75% reduction from baseline in EASI (EASI-75) and associated 95% CI (using the Clopper-Pearson method) will be reported descriptively.

All EASI assessments will be listed. A line graph presenting the value in EASI and a line graph presenting the change from baseline in the EASI over time will be produced.

12.4.4 Total BSA Affected by AD

The overall BSA affected by AD (total BSA%) will be presented by visit, and the corresponding change and percent change from baseline when appropriate. The 95% CI will be provided for the mean change and percent change. All total BSA affected assessments will be listed. A line graph presenting the value and a line graph presenting the change from baseline in the total BSA affected over time will be produced.

13 SAFETY ANALYSIS

All safety analyses will be conducted using the safety analysis set.

13.1 Adverse Events

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0.

Treatment emergent adverse events (TEAEs) are derived as any AEs with onset date during or after the first study treatment dose. AEs starting on the first study treatment dosing date and related

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to a pre-dose study assessment will not be considered as TEAE. See [Appendix 2](#) for handling of completely or partially missing dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

An overall summary table of adverse events will be provided. The number of events and the number and percentage of participants who experienced AE, TEAE, TEAE at application site, TEAE by relationship, TEAE by toxicity grade, related TEAE by toxicity grade, TEAE of CTCAE Grade 3 or higher, serious TEAE, serious TEAE by toxicity grade, TEAE leading to study drug interruption, TEAE leading to study drug discontinuation, TEAE leading to study discontinuation and AE leading to death will be presented.

Unless otherwise specified, a participant experiencing the same TEAE multiple times will be counted only once for the corresponding PT. Similarly, if a participant experiences multiple TEAEs within the same SOC, the participant will be counted only once for that SOC. TEAEs will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

Frequency and percentage of participants who experience TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of participants who experience TEAE will be summarized by SOC, PT and relationship (causality). A treatment-related AE is defined as any TEAE that is assessed by the Investigator as possibly related to study treatment. TEAE that is assessed as not possibly related will be defined as not treatment-related. TEAE with an unknown relationship will be considered as treatment-related. If a participant experiences more than one TEAE within different relationship categories within the same SOC/PT, the participant will be counted once for that SOC/PT in each relationship category.

Frequency and percentage of participants who experience TEAE will be summarized by SOC, PT and intensity grade. TEAE with an unknown intensity grade will be considered missing. If a participant experiences more than one TEAE within different intensity grade categories within the same SOC/PT, the participant will be counted once for that SOC/PT in each intensity grade category. Similarly, frequency and percentage of participants who experience treatment-related TEAE will be summarized by SOC, PT and intensity grade.

Frequency and percentage of participants who experience serious TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of participants who experience TEAE of intensity of Grade 3 or higher will be summarized by SOC and PT within SOC.

Frequency and percentage of participants who experience serious TEAE will be summarized by SOC, PT and intensity grade. TEAE with an unknown intensity grade will be considered missing.

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If a participant experiences more than one TEAE within different intensity grade categories within the same SOC/PT, the participant will be counted once for that SOC/PT in each intensity grade category.

Frequency and percentage of participants who experience Application Site TEAE will be summarized by SOC and PT.

Frequency and percentage of participants who experience TEAE of Application site pain Preferred Term will be summarized by Lowest Level Term.

Listings of all AEs, all AEs leading to death, all serious AEs, all TEAEs leading to study treatment discontinuation, all TEAEs leading to study treatment interruption and all TEAEs leading to study discontinuation will be provided. A listing of drug overdose will be provided.

13.2 Clinical Laboratory

Descriptive statistics will be presented for data related to serum chemistry, hematology and quantitative urinalysis. Change from baseline values will be presented for each post-baseline assessment. Frequencies and percentages for each result will be provided for qualitative urinalysis data.

Shift tables from baseline to each post-baseline visits describing shifts to abnormality will be provided as well based on abnormality in the CRF. Only participants with a baseline result and a result at the specified visit for the parameter will be considered.

Separate listings of all data for serum chemistry, hematology and urinalysis will be provided. Pregnancy tests results will be listed.

In addition, separate listings of data for serum chemistry, hematology and urinalysis will be provided for each parameter where a participant had at least one abnormal clinically significant result.

13.3 Vital Signs

Descriptive statistics will be presented for data related to vital signs (systolic blood pressure diastolic blood pressure, pulse, respiratory rate and body temperature). A listing of all vital signs assessments will be provided.

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14 REFERENCES

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15 APPENDICES

Appendix 1

Output Conventions

TLF will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1 inch margins and 9 pt Courier New font.

The header section will comprise the Sponsor's name, the protocol number, the delivery description, the data cut-off date (if applicable), the TLF number, the TLF title, the analysis set, and the page number (Page X of Y). The footer section will include the TLF footnotes, the CRO's name, the date and time of the execution of the program, the reference listings and the name of the program.

Mean, median and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; standard deviation, standard error and CI will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as “<0.1”. The denominator for each percentage will be the number of participants within the population per treatment group unless otherwise specified.

Listings will be ordered by participant number, date and visit (where applicable). Imputed dates will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Presentation of Treatment Groups

When applicable, study treatments will be represented as follows in the different outputs:

Study Treatment Full Name	Study Treatment Output Name
Ruxolitinib 1.5% BID	Ruxolitinib

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Appendix 2

Algorithm for Imputation of Start/End Date of Adverse Events, Prior/Concomitant Medications and Prior/Concomitant Non-Drug Therapies and Surgical Procedures

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date.
- Completely missing: Impute to the first study treatment date.
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date.
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date.
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event End Date Imputation

- Completely Missing: Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.

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Appendix 3

Scoring Method for the Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100. Of note, a score can be computed for a domain only if no more than one item is missing from that domain. The calculations specific to each domain are presented in detail below.

1. Global Satisfaction

$([\text{Sum}(Item\ 7\ \text{to}\ Item\ 9) - 3] \text{ divided by } 14) * 100$

If either Item 7 or 8 is missing

$([\text{Sum}(\text{the two completed items}) - 2] \text{ divided by } 10) * 100$

If Item 9 is missing

$([\text{Sum}(Item7\ \text{and}\ Item8)) - 2] \text{ divided by } 8) * 100$

2. Effectiveness

$([\text{Item}\ 1 + \text{Item}\ 2 + \text{Item}\ 3) - 3] \text{ divided by } 18) * 100$

If one item is missing

$([\text{Sum}(\text{the two completed items} - 2] \text{ divided by } 12) * 100$

3. Convenience

$([\text{Sum}(Item\ 4\ \text{to}\ Item\ 6) - 3] \text{ divided by } 18) * 100$

If one item is missing

$([\text{Sum}(\text{the two completed items}) - 2] \text{ divided by } 12) * 100$

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Appendix 4

Scoring Method for the Eczema Area and Severity Index

Four anatomic sites (head, upper extremities, trunk, and lower extremities) are assessed for erythema, induration/infiltration (papules), excoriation, and lichenification as seen on the day of the examination. The severity of each sign is assessed using the following 4-point scale (half steps are allowed; eg, 0.5, 1.5, and 2.5):

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The area affected by AD within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of AD involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to < 30%
- 3 = 30% to < 50%
- 4 = 50% to < 70%
- 5 = 70% to < 90%
- 6 = 90% to 100%

The EASI score is obtained by using the following formula:

$$\text{EASI} = 0.1 (E_h + I_h + Ex_h + L_h) A_h + 0.2 (E_u + I_u + Ex_u + L_u) A_u + 0.3 (E_t + I_t + Ex_t + L_t) A_t + 0.4 (E_l + I_l + Ex_l + L_l) A_l.$$

Where E, I, Ex, L, and A denote erythema, induration, excoriation, lichenification, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

The EASI score will be set as missing if at least one question value is missing.

Certificate Of Completion

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Status: Completed

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Source Envelope:

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In Person Signer Events	Signature	Timestamp
Editor Delivery Events	Status	Timestamp
Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
[Redacted] [Redacted]	COPIED	Sent: 06-Oct-2022 10:17

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Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	05-Oct-2022 15:44
Certified Delivered	Security Checked	06-Oct-2022 10:16
Signing Complete	Security Checked	06-Oct-2022 10:17
Completed	Security Checked	06-Oct-2022 10:17

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