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Statistical Analysis Plan

INCB 18424-319/320

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Prurigo Nodularis

Topical **Ru**xolitinib **E**valuation in **P**rurigo **N**odularis (TRuE-PN1/2)

IND Number:	**77101**
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Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Protocol Versions:	**INCB 18424-319 Protocol Amendment 4 dated 21 FEB 2024** **INCB 18424-320 Protocol Amendment 2 dated 21 FEB 2024**
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SAP Version:	**Original**
SAP Author:	[redacted] [redacted]**, Biostatistics**
Date of Plan:	**15 JUL 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
AE	adverse event
ASR	application site reaction
BID	twice daily
BMI	body mass index
BSA	body surface area
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
EOT	end of treatment
EQ-5D-5L	EuroQol 5-dimension 5-level scale
EQ VAS	EuroQol visual analogue scale
ET	early termination
FACIT	Functional Assessment of Chronic Illness Therapy
HADS	Hospital Anxiety and Depression Scale
IGA-CPG-A	Investigator Global Assessment for Activity of Chronic Prurigo
IGA-CPG-A-TS	Investigator's Global Assessment for Activity of Chronic Prurigo Treatment Success
IGA-CPG-S	Investigator Global Assessment for Stage of Chronic Prurigo
IGA-CPG-S-TS	Investigator's Global Assessment for Stage of Chronic Prurigo Treatment Success
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NRS	numeric rating scale
OLE	open-label extension
PAS	Prurigo Activity Score
PD	pharmacodynamic(s)
[redacted]	
PK	pharmacokinetic(s)
PN	prurigo nodularis
PP	per Protocol

Abbreviation	Term
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System®
PT	preferred term
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TS	treatment success
WHO	World Health Organization
WI-NRS	Worst-Itch Numeric Rating Scale
WI-NRS4	≥ 4-point improvement in WI-NRS score
WPAI	Work Productivity and Activity Index

1. INTRODUCTION

INCB 18424-319 is a Phase 3, multicenter, randomized, DBVC, parallel-group study in adults with PN (IGA-CPG-S score of ≥ 2; ≥ 6 pruriginous lesions on ≥ 2 different body areas; and PN-related WI-NRS score ≥ 7). Approximately 180 participants will be randomized 1:1 to 1 of 2 treatment groups (ruxolitinib 1.5% cream BID or vehicle cream BID) stratified by baseline IGA-CPG-S score (2 or ≥ 3) and geographic region (North America or outside of North America). Participants with an IGA-CPG-S score of 2 will constitute up to approximately 20% of the overall study population.

Participants will apply blinded study treatment for 12 weeks followed by a 40-week OLE period. During the OLE period, all participants, including those initially randomized to vehicle, will apply ruxolitinib 1.5% cream BID. A 30-day post-treatment, safety follow-up visit will be conducted after the OLE period.

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, and the Department of Clinical Pharmacokinetics or designee will execute the analyses of PK.

Another Phase 3 study, INCB 18424-320, has a study design identical to INCB 18424-319. This SAP applies to both the INCB 18424-319 and INCB 18424-320 studies.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 18424-319 Protocol Amendment 4 and INCB 18424-320 Protocol Amendment 2, both dated 21 FEB 2024; INCB 18424-319 CRF approved 16 FEB 2024; and INCB 18424-320 CRF approved 04 APR 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 demonstrate the efficacy of ruxolitinib 1.5% cream BID in participants with PN.	WI-NRS4 response at Week 12, defined as achieving a ≥ 4-point improvement (reduction) in WI-NRS score from baseline.
Key Secondary	
To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at Week 4. • Overall-TS at Week 12, defined as achieving both a WI-NRS4 response and an IGA-CPG-S-TS. (IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline) • IGA-CPG-S-TS at Week 12. • WI-NRS4 response on Day 7.
Secondary	
To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at each postbaseline visit. • Change from baseline in WI-NRS score at each postbaseline visit. • Time to ≥ 2-point improvement from baseline in WI-NRS score. • Time to ≥ 4-point improvement from baseline in WI-NRS score. • Achieving a ≥ 2-point improvement (reduction) in Skin Pain NRS score from baseline. • Change from baseline in Skin Pain NRS score at each postbaseline visit. • IGA-CPG-S-TS at each postbaseline visit. • IGA-CPG-A score of 0 or 1 with a least a 2-grade improvement (reduction) at each postbaseline visit. • Achieving > 75% healed lesions from PAS at each postbaseline visit.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
To evaluate the effect of ruxolitinib 1.5% cream BID on QOL.	• Change from baseline in DLQI score at each postbaseline visit. • Change from baseline in EQ-5D-5L score at each postbaseline visit.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID in participants with PN.	The type, frequency, and severity of AEs, including changes in vital signs and clinical laboratory blood samples.
Exploratory	
[redacted]	

3. STUDY DESIGN

This is a Phase 3, multicenter, randomized, DBVC, parallel-group study in adults with PN (IGA-CPG-S score of ≥ 2; ≥ 6 pruriginous lesions on ≥ 2 different body areas; and PN-related WI-NRS score ≥ 7). The study will consist of a 12-week DBVC period followed by a 40-week OLE period.

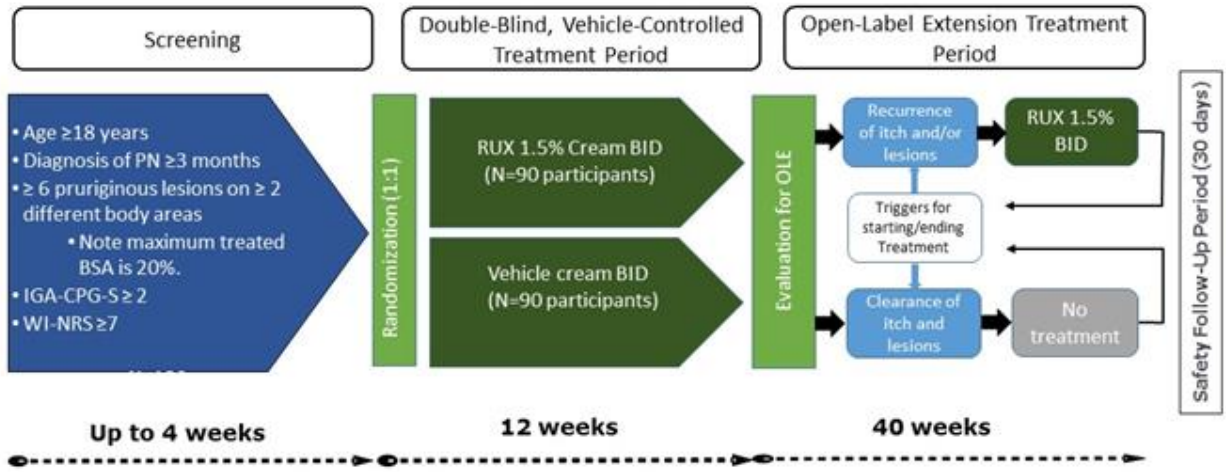
Participants will be screened for up to 4 weeks prior to the first application of study cream. Approximately 180 eligible participants will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream. Participants will be stratified by baseline IGA-CPG-S score (2 or ≥ 3) and geographic region (North America or outside of North America). Participants will apply either ruxolitinib 1.5% cream BID or vehicle cream BID through Week 12 to all pruriginous lesions identified at baseline.

At Week 12, participants who have completed 12 weeks of treatment with no safety concerns will enter the 40-week OLE period. Participants randomized to vehicle cream BID at baseline will be crossed over to ruxolitinib 1.5% cream BID and participants randomized to ruxolitinib 1.5% cream BID at baseline will remain on ruxolitinib 1.5% cream BID through Week 52. Participants will enter the 30-day safety follow-up period after the EOT/ET visit.

During the OLE period, starting at the Week 12 visit, pruriginous lesions will be evaluated by the investigator to confirm whether the participant still requires continuation of therapy (ie, IGA-CPG-S score ≥ 1 and/or the presence of itching related to PN). Participants with an IGA-CPG-S score of 0 may continue or restart therapy if there is itch associated with underlying PN, or they can otherwise (re)enter the observation/no-treatment cycle (ie, IGA-CPG-S score of 0 and WI-NRS score of 0).

The study design schema is shown in Figure 1.

Figure 1: Study Design Schema



RUX = ruxolitinib.

The primary analysis will occur after the primary database lock, when all participants have completed or discontinued from the DBVC period. The final analysis will occur when all participants have completed or withdrawn from the study.

3.1. Randomization

Approximately 180 participants will be randomized 1:1 to either ruxolitinib 1.5% cream BID or vehicle cream BID. Participants will be stratified by baseline IGA-CPG-S score (2 or ≥ 3) and geographic 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 a 2-sided $\alpha = 0.05$ level in the following order:

1. WI-NRS4 response at Week 12
2. WI-NRS4 response at Week 4
3. Overall-TS at Week 12, defined as achieving both WI-NRS4 response and IGA-CPG-S-TS
4. IGA-CPG-S-TS at Week 12
5. WI-NRS4 response on 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 calculation is based on the Fisher exact test for the primary efficacy endpoint, which is the proportion of participants with WI-NRS4 response at Week 12. The mechanism of stopping the itch-scratch cycle and reducing the pruritus are similar between PN and AD. Additionally, based on the results from the following nemolizumab studies: a Phase 2 study in AD (Silverberg et al 2020), a Phase 2 study in PN (Galderma 2021), and a Phase 3 study in PN (Galderma 2022), the improvement in WI-NRS is not substantially different between AD and PN. Therefore, the results from 2 Phase 3 studies (INCB 18424-303 and INCB 18424-304) of ruxolitinib cream in the treatment of AD are used to build the assumptions of the proportion of participants with WI-NRS4 response, which are 50% for ruxolitinib 1.5% cream BID and 25% for vehicle cream BID. Using a 2-sided $\alpha = 0.05$, the sample size based on the current assumption will have > 90% power to detect a difference between ruxolitinib cream and vehicle cream. In addition, the assumptions and powers for key secondary endpoints are provided in Table 2.

Table 2: Powering for Key Secondary Endpoints

Variables	Response Rates in Ruxolitinib 1.5% BID	Response Rates in Vehicle BID	Power: 1.5% BID vs Vehicle BID
WI-NRS4 response at Week 4	40%	15%	> 90%
Overall-TS (WI-NRS4 response and IGA-CPG-S-TS) at Week 12	30%	10%	> 90%
IGA-CPG-S-TS at Week 12	40%	20%	80%
WI-NRS4 response on Day 7	30%	10%	> 90%

Note: Based on Fisher's exact test, 2-sided $\alpha = 0.05$.

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

3.4. Schedule of Assessments

Refer to INCB 18424-319 Protocol Amendment 4 and INCB 18424-320 Protocol Amendment 2 dated 21 FEB 2024 for a full description of all study procedures and assessment schedules.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date of the first application of ruxolitinib 1.5% cream or vehicle cream in the specific treatment period.

For randomized participants not treated with any study cream, Day 1 is defined as the date 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

For the DBVC period, baseline is the last nonmissing measurement obtained before or on the day of the first application of ruxolitinib 1.5% cream or vehicle cream in the DBVC period, unless otherwise defined.

For randomized participants not treated with any study cream, baseline is defined as the last nonmissing assessment before or on the date of randomization.

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

- For efficacy evaluations in the OLE period, baseline is the last nonmissing measurement obtained before or on the day of the first application of study treatment in the DBVC period.
- For safety evaluations in the OLE period, baseline is the last nonmissing measurement obtained before or on the day of the first application of ruxolitinib 1.5% cream in the study.

When a scheduled assessment and an unscheduled assessment occur on the same day and the times of the assessments are 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 the scheduled assessment is missing on the day of the first application and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

A partial PN diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis date is completely missing, then the time since diagnosis will not be calculated.

When the date of the last application is used in deriving variables, such as duration of treatment or TEAE flag, a missing date of the last application in the specified treatment period will be handled as follows:

- If the last application date is missing, then the end date of the specified treatment period will be used as the date of the last application.
- If the last application date and the end date of the specified treatment period are both missing and the participant is lost to follow-up, then the date of last contact will be used as the date of the last application.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medications

A prior medication is defined as any nonstudy medication started before the first application of ruxolitinib 1.5% cream or vehicle cream.

A concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first application of ruxolitinib 1.5% cream or vehicle cream and is ongoing throughout the study or ends on/after the date of first study cream application.
- On/after the date of first application of ruxolitinib 1.5% cream or vehicle cream and is ongoing or ends during the course of the study.

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 ruxolitinib 1.5% cream or vehicle cream. In the listing, it will be indicated whether a medication is only prior, only concomitant, 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; v9.4 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, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

5.2. Treatment Groups

This is a randomized study with DBVC and OLE periods.

Efficacy data will be presented by treatment group assigned at study entry. The treatment groups will be ruxolitinib 1.5% cream BID and vehicle cream BID.

Safety data will be presented by the actual treatment participants applied as follows.

- For safety data in the DBVC period, the treatment groups will be ruxolitinib 1.5% cream BID and vehicle cream BID.
- For safety data in the OLE period, the treatment groups will be ruxolitinib 1.5% cream BID to ruxolitinib 1.5% cream BID and vehicle cream BID to ruxolitinib 1.5% cream BID.
- For safety data throughout the study, the only treatment group will be ruxolitinib 1.5% cream BID, including only participants who applied ruxolitinib 1.5% cream BID from Day 1 through Week 52 or end of study treatment.

5.3. Analysis Populations

5.3.1. Intent-to-Treat Population

All participants who are randomized 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 cream the participant might apply during their participation in the DBVC period.

The ITT Population will be used for the summary of demographics, baseline characteristics, participant disposition, medical history, prior and concomitant medications, and analyses of all efficacy data, unless otherwise specified.

5.3.2. Per Protocol Population

The PP Population will include randomized participants who are considered to be sufficiently compliant with the Protocol. It is defined for the supportive analysis for primary efficacy endpoint in the DBVC period. Participants with important Protocol deviations, as defined below, will be excluded from the PP Population.

In general, the following are important Protocol deviations that may have an essential impact on the primary analysis:

- Missing primary endpoint data (ie, WI-NRS score at Week 12) for any reason, including early withdrawal from the DBVC period.
- Study cream application compliance, as defined in Section 6.5, is below 60%.

In addition, Protocol deviations related to inclusion/exclusion criteria, discontinuation criteria, and use of prohibited medications will be reviewed. Decisions as to whether any of these deviations warrant exclusion from the PP Population will be made before the unblinding of the study.

5.3.3. Safety Population

The Safety Population will include all participants who applied ruxolitinib 1.5% cream or vehicle cream at least once. Treatment groups for this population will be determined according to the actual treatment the participant applied on Day 1 regardless of assigned treatment group.

The Safety Population will be used for safety summaries in the DBVC period.

5.3.3.1. Open-Label Extension Safety Population

The OLE Safety Population will include all participants who applied ruxolitinib 1.5% cream at least once during the OLE period.

All safety analyses conducted specifically for the OLE period will use the OLE Safety Population.

5.3.4. Pharmacokinetic-Evaluable Population

The PK-Evaluable Population will include participants who applied ruxolitinib 1.5% cream at least once and provided at least 1 postbaseline blood sample for PK analysis. The study pharmacokineticist will review data listings of participant application and sample records to identify participants to be excluded from the analysis.

5.3.5. Pharmacodynamic-Evaluable Population

The PD-Evaluable Population will include participants who applied study cream at least once and provided a baseline PD sample and at least 1 postbaseline PD sample for analysis. The study translational scientist will review data listings of participant application and sample records to identify participants to be excluded from the analysis.

5.3.6. Pharmacokinetic/Pharmacodynamic Evaluable Population

The PK/PD-Evaluable Population will include all participants who are in both the PK-Evaluable and PD-Evaluable Populations, as well as participants who are PD-evaluable while receiving vehicle cream during the DBVC period.

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 and baseline characteristics will be summarized by treatment group and overall for the ITT Population in the DBVC period and for the OLE Safety Population in the OLE period: age, sex, race, ethnicity, weight, height, and BMI.

6.1.2. Baseline Disease Characteristics

For the ITT Population, the baseline disease characteristics will be summarized and analyzed by treatment group and will include but not be limited to the following:

- Disease duration (months)
- Prior history of atopic medical conditions (atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, food allergy, drug allergy, urticaria, anaphylaxis, and other)
- PN family history (yes/no)
- Skin type based on Fitzpatrick Scale
- PN-related skin infection requiring antibiotic treatment (yes/no)
- Days since onset of current episode of PN
- Prior treatment received for the current episode (yes/no)
- By-visit WI-NRS score at baseline
- By-visit Skin Pain NRS score at baseline
- IGA-CPG-S score at baseline
- IGA-CPG-A score at baseline
- Total BSA involvement

6.1.3. Disease History

The time since diagnosis will be summarized for all participants in the ITT Population and will be calculated as follows:

Disease duration (months) = (date of randomization – date of initial PN diagnosis + 1) / 30.4375.

6.1.4. Medical History

For participants in the ITT Population, medical history will be summarized by assigned treatment group. This summary will include the number and percentage of participants with medical history for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participants

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

The number and percentage of participants who completed the OLE period, who discontinued treatment during the OLE period with a primary reason for discontinuation, and who withdrew from the study during the OLE period with a primary reason for withdrawal will be summarized for the OLE Safety Population.

The number of participants enrolled by country and site will also be provided by treatment group.

6.3. Protocol Deviations

For participants in the ITT Population in the DBVC period, as well as the OLE Safety Population in the OLE period, Protocol deviations recorded on the eCRF will be summarized and listed by category (critical, major, or minor) for each treatment group and overall.

6.4. Exposure

For participants in the Safety Population in the DBVC period, in the OLE Safety Population in the OLE period, and who applied ruxolitinib 1.5% cream BID throughout study participation, study cream exposure will be summarized by treatment group descriptively with duration of treatment, total amount of cream applied, and average daily application.

6.5. Study Cream Application Compliance

The overall compliance (%) for the application of ruxolitinib 1.5% cream BID or vehicle cream BID during the DBVC period will be calculated for all participants in the Safety Population as follows:

Study cream application compliance (%) = 100 × total number of nonmissing applications / total number of intended applications

where

Total number of nonmissing applications = number of applications that the participant actually applied during the study

and

Total number of intended applications = 2 × duration of treatment (days) – number of interrupted applications

6.6. Prior and Concomitant Medications

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of participants with prior and concomitant medications will be summarized by treatment group and overall for the ITT Population during the DBVC period by WHO drug class and the WHO drug preferred term. For the OLE period, only concomitant medications will be summarized based on OLE Safety Population.

7. EFFICACY

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

7.1. Efficacy Hypothesis

The primary hypothesis is that in participants with PN, ruxolitinib 1.5% cream BID is superior to vehicle cream BID with regard to the WI-NRS4 response rate at Week 12. Assume *OR* is the common odds ratio between the treatment groups for the proportion of WI-NRS4 responses at Week 12. The following are the primary hypotheses of the study:

- H_0 (null hypothesis): $OR = 1$
- H_A (alternative hypothesis): $OR \neq 1$

7.2. Efficacy Measures

7.2.1. Worst-Itch Numeric Rating Scale

The WI-NRS is a PRO comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch"). Each evening beginning on the day of screening through Week 52 or ET, the participant will assess their worst level of PN-related itch during the past 24 hours on a scale of 0 to 10 in an eDiary.

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

7.2.2. Investigator's Global Assessment

The severity and the activity of PN will be assessed via the IGA-CPG-S and the IGA-CPG-A, respectively.

7.2.2.1. Investigator Global Assessment for Stage of Chronic Prurigo

The IGA-CPG-S is an overall severity rating on a scale of 0 to 4 (see Table 3).

Table 3: IGA-CPG-S

Score	Category	Description: Stage
0	Clear	No lesions (0 lesions)
1	Almost clear	Rare palpable pruriginous lesions (approximately 1-5 lesions)
2	Mild	Few palpable pruriginous lesions (approximately 6-19 lesions)
3	Moderate	Many palpable pruriginous lesions (approximately 20-100 lesions)
4	Severe	Abundant palpable pruriginous lesions (over 100 lesions)

Source: Zeidler et al 2021.

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

7.2.2.2. Investigator Global Assessment for Activity of Chronic Prurigo

The IGA-CPG-A is an overall severity rating on a scale of 0 to 4 (see Table 4).

Table 4: IGA-CPG-A

Score	Category	Description: Activity
0	Clear	No pruriginous lesions have excoriations or crusts
1	Almost clear	Very small proportion of pruriginous lesions have excoriations or crusts (up to approximately 10% of all pruriginous lesions)
2	Mild	Minority of pruriginous lesions have excoriations or crusts (approximately 11%-25% of all pruriginous lesions)
3	Moderate	Many pruriginous lesions have excoriations or crusts (approximately 26%-75% of all pruriginous lesions)
4	Severe	Majority of pruriginous lesions have excoriations or crusts (approximately 76%-100% of all pruriginous lesions)

Source: Zeidler et al 2021.

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

7.2.3. Prurigo Activity Score

The extent and severity of PN will also be assessed via the PAS (v1.2). The first 3 items are descriptive of the type, predominant type, distribution, and quantity of pruriginous lesions. The remaining 2 items of the PAS will assess disease activity in terms of percentage (ie, 0%, 1%-25%, 26%-50%, 51%-75%, and 76%-100%) of pruriginous lesions with excoriations/crusts on top (to reflect active scratching) and the percentage (ie, 100%, 76%-99%, 51%-75%, 26%-50%, and 0%-25%) of healed pruriginous lesions in order to quantify change of PN skin lesions. In addition, the total number of pruriginous lesions in a representative area will be identified at screening and followed throughout the study.

7.2.4. Body Surface Area

Total estimation of the %BSA treatment area will be used to determine the number of tubes of study cream dispensed at each visit. Treatment area is defined as the area affected by pruriginous lesions plus an approximate 1-cm area surrounding each lesion. Body surface area assessment will be approximated to the nearest 0.1% using the palmar method as a guide. The palmar method is the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), which is considered as 1% BSA, and the thumb is considered 0.1% BSA.

7.2.5. Other Patient-Reported Outcomes

Patient-reported outcomes will be assessed at designated visits as outlined in the Protocol.

For all PRO assessments conducted at the study site, in order to avoid bias in the participants' responses to the questionnaires, assessments should be completed before any other evaluations or study procedures on the day of the study visit and prior to treatment-related discussions with the investigator or study site staff.

7.2.5.1. Skin Pain Numeric Rating Scale

Participants will be instructed to complete and record the Skin Pain NRS in a diary each evening, beginning on the day of screening through Week 52 or treatment discontinuation, whichever comes first. The participants will assess their worst level of PN-related skin pain during the past 24 hours on a scale of 0 to 10.

The Skin Pain NRS score for baseline will be determined by averaging the 7 daily NRS scores before Day 1 (ie, Days −7 to −1) for all by-visit summaries. The by-visit 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 Skin Pain NRS score at the visit will be set to missing. For all daily pain-related analyses, baseline will be defined as the last available daily pain NRS score during the last week prior to Day 1 (ie, Days −7 to −1).

7.2.5.2. Dermatology Life Quality Index

The DLQI is a simple, 10-question, validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days (Finlay and Khan 1994).

The scoring of each question will be as follows: 3 (very much), 2 (a lot), 1 (a little), 0 (not at all or not relevant).

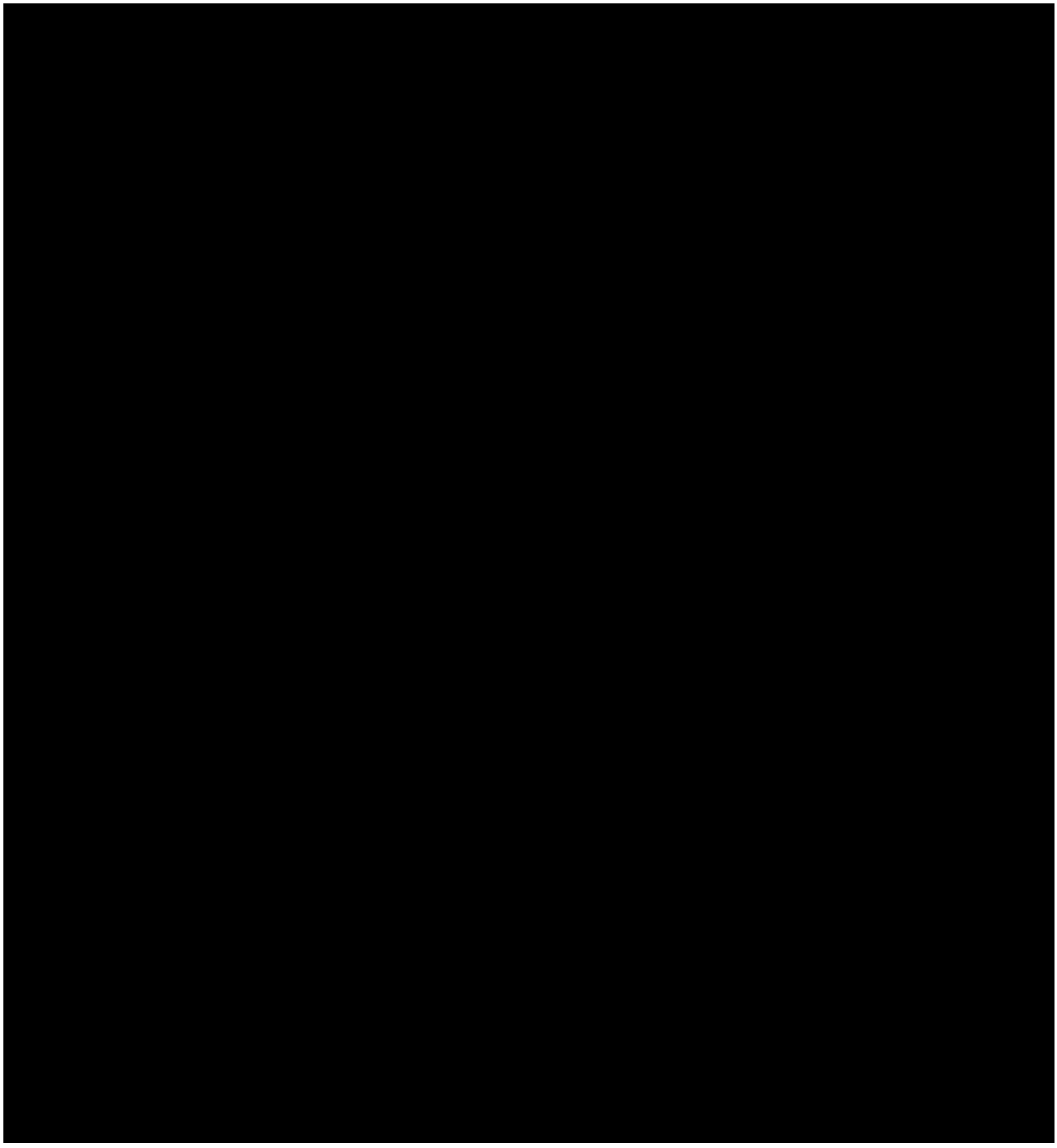
The following imputation will be applied for those questionnaires considered incomplete:

- If 1 question is left unanswered, then this is scored as 0; the scores will be summed and expressed as usual (ie, out of a maximum of 30).
- If 2 or more questions are left unanswered, the questionnaire will not be scored.
- For Question 7, the following criteria applies:
  - If answered "yes," then the score will be 3.
  - If answered "no," but then either "a lot" or "a little" is ticked, then the score will be either 2 or 1, respectively.
  - If answered "not relevant," then the score will be 0.
  - If answered "no," but the second half is left incomplete, then the score will remain 0.
- If 2 or more response options are ticked, the response option with the highest score will be recorded.
- If there is a response between 2 tick boxes, the lower of the 2 score options will be recorded.
- For DLQI 6 subscales, if the answer to one question in a subscale is missing, that subscale will not be scored.

The DLQI total score will be 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 the quality of life is impaired.

Total DLQI scores are categorized as follows: 0 to 1 (no effect), 2 to 5 (small effect), 6 to 10 (moderate effect), 11 to 20 (very large effect), and 21 to 30 (extremely large effect).

The questionnaire is also analyzed under the following 6 subscales: symptoms and feelings (Questions 1 and 2), daily activities (Questions 3 and 4), leisure (Questions 5 and 6), work and school (Question 7), personal relationships (Questions 8 and 9), and treatment (Question 10).



[redacted]

7.2.5.9. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (Herdman et al 2011). The EQ-5D-5L will provide data for use in economic models and analyses including the development of health utilities or quality-adjusted life-years.

The EQ-5D-5L consists of 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), on which the endpoints are labeled "the best health you can imagine" (100 score) and "the worst health you can imagine" (0 score).

The categorical outcomes on the 5 dimensions of EQ-5D will be summarized. Additionally, the change from baseline in EQ VAS score will be analyzed.

[redacted]

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

The primary analysis will be based on the ITT Population in the DBVC period. A summary of the primary endpoint analysis is provided in Table 5.

Table 5: Summary of Primary Analysis

Parameter	Definition
Treatment	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT Population
Variable	WI-NRS4 response at Week 12
Population-level summary	WI-NRS4 response rate difference with 95% CI

Note: Participants with missing Week 12 data for any reason, including treatment discontinuation (due to development of AD lesions or any other cause), will be defined as nonresponders. No rescue therapy is allowed in this study.

The WI-NRS score at each postbaseline visit (ie, the by-visit WI-NRS score), 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 WI-NRS score at the visit will be set to missing. Missing WI-NRS scores at each postbaseline visit will be imputed as nonresponders for the primary analysis. The baseline for the by-visit WI-NRS score will be determined by averaging the 7 daily NRS scores before Day 1 (ie, Day −7 to Day −1). The proportion of participants with a WI-NRS4 response, defined as achieving a ≥ 4-point improvement in the by-visit WI-NRS score from baseline, will be summarized by treatment group and visit.

The primary hypothesis specified in Section 7.1 will be tested at a 2-sided $\alpha = 0.05$ level using a CMH test stratified by IGA-CPG-S score (2 or ≥ 3) and geographic region (North America or outside of North America). The p-value and stratum-adjusted WI-NRS4 response rate difference with the 95% CI will be provided. An overall odds ratio will also be provided with the 95% CI.

7.3.2. Subgroup Analyses for Primary Endpoint

Subgroups will be formed based on the following participant characteristics and baseline variables for those participants whose data are available:

- Baseline IGA-CPG-S score: 2 or ≥ 3
- Geographic region: North America or outside of North America
- Sex: female or male
- Race: White/Caucasian, Black or African American, or Asian and Others
- Age group: 18 to < 65 years or ≥ 65 years
- Ethnicity: Hispanic or Latino or Not Hispanic or Latino and Others

The primary endpoint will be summarized and analyzed using descriptive statistics based on the ITT Population for the aforementioned subgroups in the DBVC period.

7.3.3. Supportive and Sensitivity Analyses for the Primary Endpoint

7.3.3.1. Per Protocol Population Analysis

Supportive analysis will be performed for the PP Population (defined in Section 5.3.2) using the same method as the primary analysis.

7.3.3.2. Longitudinal Logistic Regression With Repeated Measures

To adjust for the dependence underlying the hierarchical multilevel data structure (ie, visit, participant, and site), a longitudinal logistic regression with repeated measures will be applied. In the model, visits are nested within participants, which are further nested within sites.

The primary endpoint binary response of the participant at each of the postbaseline scheduled visits up to Week 12 will be included as the dependent variable. Treatment (ruxolitinib 1.5% cream BID and vehicle cream BID), randomization stratification factors, visit, and treatment by visit interaction will be included as fixed effects. Site-level intercept and participant nested in site-level intercept will be included as random effects. The within-participant and within-site errors will be modeled by an unstructured variance-covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for this model.

7.3.3.3. Multiple Imputation

A fully conditional specification method (van Buuren 2007) that assumes the existence of a joint distribution for all variables will be used to impute missing 7-day average WI-NRS scores at each visit. A regression model, including treatment group, stratification factors, baseline WI-NRS score, and WI-NRS scores for each scheduled postbaseline visit up to Week 12, will be specified for the fully conditional specification method. The imputation will be repeated 30 times to generate corresponding complete data sets in order to reflect the uncertainty around the true values. Random seeds of "18424319" for the INCB 18424-319 study and "18424320" for the INCB 18424-320 study will be used for the multiple imputation. After the missing values are imputed, the binary variables will be derived based on the definition. The CMH test similar to that for the primary analysis will be applied to each imputed dataset for comparison at Week 12, and the results will then be combined for inference using Rubin's rule.

7.3.3.4. Tipping Point Analysis

A tipping point analysis will be conducted to examine the potential effects of missing data. A missing binary response for the primary endpoint in each treatment group will be replaced by a range of values from the most conservative case to the most aggressive case. The most conservative case is that all the missing participants in the ruxolitinib cream group are nonresponders and all the missing participants in the vehicle cream group are responders, while the most aggressive case is the reverse. For each scenario, between-treatment comparisons will be performed using the Fisher exact test.

7.4. Analysis of the Key Secondary Efficacy Parameters

All key secondary efficacy analyses will be conducted on the ITT Population in the DBVC period.

If the primary objective is achieved, the statistical hypotheses for the following key secondary endpoints will be tested in a fixed sequence at a 2-sided $\alpha = 0.05$ level in the following order:

1. WI-NRS4 response at Week 4
2. Overall-TS at Week 12
3. IGA-CPG-S-TS at Week 12
4. WI-NRS4 response on Day 7

The statistical comparisons for the key secondary endpoints, WI-NRS4 at Week 4, Overall-TS at Week 12, and IGA-CPG-S-TS at Week 12, will be analyzed using the similar method as specified in the primary analysis. Missing values at each visit will be imputed as nonresponders.

For the composite endpoint Overall-TS, defined as achieving both a WI-NRS4 response and an IGA-CPG-S-TS, the by-visit WI-NRS score (as defined in Section 7.3.1) will be used to derive the Overall-TS response.

For the WI-NRS4 response on Day 7, daily WI-NRS scores will be used for the analysis. Baseline will be defined as the last available daily WI-NRS score during the last week prior to Day 1 (ie, Days −7 to −1). Missing daily WI-NRS scores from Day 1 to Day 7 will be imputed using the similar multiple imputation method as outlined in the sensitivity analysis for the primary endpoint. Specifically, a regression model, including treatment group, stratification factors, baseline daily WI-NRS score, and daily WI-NRS scores from Day 1 to Day 7, will be specified for the fully conditional specification method. For each imputed dataset, the proportion of participant with an WI-NRS4 response on Day 7, defined as a $\geq$ 4-point improvement (reduction) in daily WI-NRS score from baseline to Day 7, will be analyzed using the CMH test as specified for the primary analysis. Then the results will be combined for inference using Rubin's rule.

7.5. Analysis of the Other Secondary Efficacy Parameters

All other secondary efficacy analyses will be conducted for the ITT Population in the DBVC period.

7.5.1. Continuous Efficacy Endpoints

The summary and analysis of statistics for the following continuous parameters, including change and percentage change (if applicable) from baseline, will be presented by treatment group and visit:

- By-visit WI-NRS score
- By-visit Skin Pain NRS score
- DLQI total and subscale scores
- EQ VAS score

The summary statistics include sample size, mean, median, standard deviation, minimum, maximum, first quartile, third quartile, and 95% CI. A mixed model for repeated measures with the fixed effect of the treatment group (ruxolitinib 1.5% cream and vehicle cream), randomization stratification factors, visit, and visit by treatment interaction may be fit for the comparison between ruxolitinib 1.5% cream and vehicle cream.

7.5.2. Categorical Efficacy Endpoints

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

- WI-NRS4 response
- ≥ 2-point improvement in Skin Pain NRS score from baseline
- IGA-CPG-S-TS
- IGA-CPG-A-TS
- > 75% healed lesions from PAS
- Each category of each EQ-5D-5L dimension

For the endpoint ≥ 2-point improvement in Skin Pain NRS score from baseline, the analysis will be conducted on the ITT Population in the DBVC period with a baseline Skin Pain NRS score of ≥ 2. The analysis for IGA-CPG-A-TS will be conducted on the ITT Population in the DBVC period with baseline IGA-CPG-A score of ≥ 2.

For the endpoints with binary outcomes based on WI-NRS, Skin Pain NRS, IGA-CPG-S, IGA-CPG-A, and PAS scores, missing postbaseline values will be imputed as nonresponders. A similar CMH test as specified for the primary endpoint may be fit for the binary endpoints at Week 12 visit.

7.5.3. Time-to-Event Endpoints

For the following time-to-event endpoints, daily WI-NRS scores during the DBVC period will be used for the analysis:

- Time to ≥ 2-point improvement from baseline in WI-NRS score
- Time to ≥ 4-point improvement from baseline in WI-NRS score

A log-rank test stratified by randomization stratification factors will be used for between–treatment group comparisons. The hazard ratio and 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 group. The number of participants, number of events, and number of censoring will be summarized by treatment group. The Kaplan-Meier estimate of median time will be presented with the 95% CI, which will be calculated using the method by Brookmeyer and Crowley (1982).

7.6. Analysis of Exploratory Efficacy Parameters

[redacted]

8.2. Pharmacodynamic

Expression of select biomarkers in the skin and peripheral blood at baseline and Week 12 will be summarized by descriptive statistics by treatment group. The purpose of these analyses will be to retrospectively evaluate biomarkers related to treatment and/or the biology of disease alone and in the context of treatment.

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 period, the OLE Safety Population in the OLE period, and those who applied ruxolitinib 1.5% cream throughout the study, unless otherwise specified. 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 preferred terms 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 cross over treatments, the first application date is period-specific; 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 cream application.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0. 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 cream will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study cream, the AE will be considered to be treatment-related. The incidence of AEs and treatment--related AEs will be tabulated. In addition, serious TEAEs 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.

9.2.2. Adverse Events of Interest

Treatment-emergent AEs of interest will be summarized in the following categories:

- Cytopenias
  - Anemia
  - Thrombocytopenia
  - Neutropenia
- Herpes zoster
- Viral skin infections
- Serious infections
- Liver function test elevations
- Malignancies, excluding nonmelanoma skin neoplasms
- Nonmelanoma skin neoplasms
- Major adverse cardiovascular events
- Venous and arterial thromboembolic events
- ASRs

9.2.3. Adverse Event Summaries

An overall summary of AEs by treatment group will include the following:

- Number (%) of participants reporting any TEAEs
- 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 treatment because of TEAEs
- Number (%) of participants who permanently discontinued study treatment because of TEAEs

- Number (%) of participants who had any fatal TEAEs
- Number (%) of participants reporting any ASRs

The following summaries will be produced by MedDRA term. If 2 or fewer participants appear in a table, a listing may be provided instead of a summary table.

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of TEAEs by MedDRA SOC, PT, and CTCAE grade category
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of treatment-related TEAEs by MedDRA SOC and PT
- Summary of treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of Grade 3 or higher treatment-related TEAEs by MedDRA SOC and PT
- Summary of treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of TEAEs leading to application interruption by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of study cream by MedDRA SOC and PT
- Summary of ASRs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs of interest

9.3. Clinical Laboratory Tests

The analyses in this section will be provided for the Safety Population in the DBVC period and the OLE Safety Population in the OLE period unless otherwise specified.

9.3.1. Laboratory Value Definitions

All laboratory assessments will be performed using a central laboratory, with the exception of urine pregnancy tests (as applicable). Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3, using the last nonmissing value collected before the first application, prioritizing scheduled assessments for baseline identification over unscheduled visits. The last record before application in the highest priority will be considered the baseline record. If there are multiple values that meet the criteria for baseline, 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

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 nonmissing laboratory values for a participant's particular test at a scheduled visit, central laboratory values have higher priority over local laboratory values. If a tie still exists, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, box-and-whisker plots will be provided for select laboratory values.

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. A shift summary will be produced for each test. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, or missing) as the denominator for the percentage in each of the categories during the study.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5.0. Shift tables will also be presented showing change in CTCAE grade from baseline to the worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who had worsening of laboratory abnormalities will be summarized by maximum severity.

9.4. Vital Signs

The analyses in this section will be provided for the Safety Population in the DBVC period and the OLE Safety Population in the OLE period unless otherwise specified. 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.

Normal ranges for vital sign values are defined in Table 6. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 6: 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	> 20 breaths/min	< 8 breaths/min

10. PLANNED ANALYSES

No formal interim analysis is planned in this study.

There are 2 formal planned analyses as follows:

- The primary analysis will occur after the primary database lock, when all participants have completed or discontinued from 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 after the primary database lock.
- The final analysis will occur when all participants have completed or withdrawn from the study.

If the p-value for the primary endpoint is deemed insignificant in the primary analysis outlined in Section 7.3.1, the study will be terminated due to a lack of demonstrable efficacy benefits for the participants.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 7.

Table 7: Statistical Analysis Plan Versions

SAP Version	Date
Original	15 JUL 2024

11.1. Changes to Protocol-Defined Analyses

Coding has been corrected for the FACIT-Fatigue scale. Each item uses a 5-point scale ranging from "0 = not at all" to "4 = very much."

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. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v1.13.

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	Standard
Baseline and Demographics Characteristics			
1.1.1	Analysis Populations	All Randomized	X
1.1.1.1	Screening Disposition	All Screened	X
1.1.2.1	Summary of Participant Disposition in the DBVC Period	ITT	X
1.1.2.2	Summary of Participant Disposition in the OLE Period	OLE Safety	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	ITT	X
1.1.4.1	Summary of Protocol Deviations in the DBVC Period	ITT	X
1.1.4.2	Summary of Protocol Deviations in the OLE Period	OLE Safety	X
1.2.1	Summary of Demographics and Baseline Characteristics	ITT	X
1.2.2	Summary of Demographics and Baseline Characteristics	OLE Safety	X
1.3	Summary of Baseline Disease Characteristics	ITT	X
1.4.1	Summary of Prior Medications	ITT	X
1.4.2	Summary of Prior Medications for Prurigo Nodularis	ITT	X
1.4.3.1	Summary of Concomitant Medications in the DBVC Period	ITT	X
1.4.3.2	Summary of Concomitant Medications in the OLE Period	OLE Safety	X
1.5	Summary of General Medical History	ITT	X
Efficacy			
2.1.1.1	Summary and Analysis of Participants Achieving WI-NRS4 in the DBVC Period	ITT	
2.1.1.1.1	Summary and Analysis of Participants Achieving WI-NRS4 by Baseline IGA-CPG-S Score	ITT	
2.1.1.1.2	Summary and Analysis of Participants Achieving WI-NRS4 by Geographic Region	ITT	
2.1.1.1.3	Summary and Analysis of Participants Achieving WI-NRS4 by Race	ITT	
2.1.1.1.4	Summary and Analysis of Participants Achieving WI-NRS4 by Age Group	ITT	
2.1.1.1.5	Summary and Analysis of Participants Achieving WI-NRS4 by Ethnicity	ITT	
2.1.1.2	Summary and Analysis of Participants Achieving WI-NRS4 From Day 1 to Week 52	ITT	
2.1.1.3	Summary and Analysis of Participants Achieving WI-NRS4 at Week 12 by Tipping Point Analysis	ITT	
2.1.1.4	Summary and Analysis of Participants Achieving WI-NRS4 in the DBVC Period	PP	

Table No.	Title	Population	Standard
2.1.2	Summary and Analysis of Participants Achieving WI-NRS4 From Day 1 to Day 14	ITT	
2.1.3.1	Summary and Analysis of By-Visit WI-NRS Score in the DBVC Period	ITT	
2.1.3.2	Summary and Analysis of By-Visit WI-NRS Score in the OLE Period	OLE Safety	
2.1.4	Summary and Analysis of Time to ≥ 2-Point Improvement in Daily WI-NRS Score From Baseline During the DBVC Period	ITT (baseline daily WI-NRS score ≥ 2)	
2.1.5	Summary and Analysis of Time to ≥ 4-Point Improvement in Daily WI-NRS Score From Baseline During the DBVC Period	ITT (baseline daily WI-NRS score ≥ 4)	
2.1.3	Summary and Analysis of Daily WI-NRS Score From Baseline to Day 14	ITT	
2.2.1	Summary and Analysis of Participants Achieving Overall-TS in the DBVC Period	ITT	
2.2.2	Summary and Analysis of Participants Achieving Overall-TS From Day 1 to Week 52	ITT	
2.3.1	Summary and Analysis of Participants Achieving IGA-CPG-S-TS in the DBVC Period	ITT	
2.3.2	Summary and Analysis of Participants Achieving IGA-CPG-S-TS From Day to Week 52	ITT	
2.4.1	Summary and Analysis of Participants Achieving IGA-CPG-A-TS in the DBVC Period	ITT	
2.4.2	Summary and Analysis of Participants Achieving IGA-CPG-A-TS From Day 1 to Week 52	ITT	
2.5.1	Summary and Analysis of By-Visit Skin Pain NRS Score in the DBVC Period	ITT	
2.5.2	Summary and Analysis of By-Visit Skin Pain NRS Score in the OLE Period	OLE Safety	
2.5.3	Summary and Analysis of Participants Achieving ≥ 2-Point Improvement in By-Visit Skin Pain NRS Score From Baseline During the DBVC Period	ITT (baseline Skin Pain NRS score ≥ 2)	
2.5.4	Summary and Analysis of Participants Achieving ≥ 2-Point Improvement in By-Visit Skin Pain NRS Score From Baseline During the OLE Period	OLE Safety (baseline Skin Pain NRS score ≥ 2)	
2.6.1	Summary and Analysis of Participants Achieving > 75% Healed Lesions From PAS in the DBVC Period	ITT	
2.6.2	Summary and Analysis of Participants Achieving > 75% Healed Lesions From PAS in the OLE Period	OLE Safety	
2.7.1.1	Summary and Analysis of DLQI Total and Subscale Scores in the DBVC Period	ITT	
2.7.1.2	Summary and Analysis of DLQI Total and Subscale Scores in the OLE Period	OLE Safety	
2.7.2	Summary and Analysis of Participants Achieving ≥ 4-Point Improvement in DLQI Total Score in the DBVC Period	ITT (baseline DLQI total score ≥ 4)	
2.8.1.1	Summary and Analysis of EQ VAS Score in the DBVC Period	ITT	
2.8.1.2	Summary and Analysis of EQ VAS Score in the OLE Period	OLE Safety	
2.8.2.1	Summary of Participants in Each Category of Each Dimension of the EQ-5D-5L in the DBVC Period	ITT	

Table No.	Title	Population	Standard
2.8.2.2	Summary of Participants in Each Category of Each Dimension of the EQ-5D-5L in the OLE Period	OLE Safety	
[redacted]			
3.2.1.X	Overall Summary of Treatment-Emergent Adverse Events	Safety/OLE Safety	X
3.2.2.X	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.3.X	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety/OLE Safety	X
3.2.4.X	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety/OLE Safety	X
3.2.5.X	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Safety/OLE Safety	X
3.2.6.X	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.7.X	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety/OLE Safety	X
3.2.8.X	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X

Table No.	Title	Population	Standard
3.2.9.X	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety/OLE Safety	X
3.2.10.X	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.11.X	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety/OLE Safety	X
3.2.12.X	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.13.X	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.14.X	Summary of Treatment-Emergent Adverse Events Leading to Application Interruption in Some or All Treated Areas by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.15.X	Summary of Treatment-Emergent Adverse Events Leading to Application Interruption in All Treated Areas by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.16.X	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Cream by MedDRA System Organ Class and Preferred Term	Safety/OLE Safety	X
3.2.17.X	Summary of Application Site Reactions by MedDRA Preferred Term in Decreasing Order of Frequency	Safety/OLE Safety	X
3.2.18.X	Summary of Treatment-Emergent Adverse Events of Interest by Category and Preferred Term	Safety/OLE Safety	X
3.3.1.1.X	Summary of Laboratory Values - Hematology	Safety/OLE Safety	X
3.3.1.2.X	Summary of Laboratory Values - Chemistry	Safety/OLE Safety	X
3.3.2.1.X	Shift Summary of Hematology Laboratory Values - to the Worst Abnormal Value	Safety/OLE Safety	X
3.3.2.2.X	Shift Summary of Chemistry Laboratory Values - to the Worst Abnormal Value	Safety/OLE Safety	X
3.3.3.1.X	Shift Summary of Hematology Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal Value	Safety/OLE Safety	X
3.3.3.2.X	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal Value	Safety/OLE Safety	X
3.4.1.x	Summary of Systolic Blood Pressure	Safety/OLE Safety	X
3.4.2.x	Summary of Diastolic Blood Pressure	Safety/OLE Safety	X
3.4.3.x	Summary of Pulse	Safety/OLE Safety	X
3.4.4.x	Summary of Respiratory Rate	Safety/OLE Safety	X
3.4.5.x	Summary of Body Temperature	Safety/OLE Safety	X

Note: For AE tables ending with ".x," separate tables will be provided for the DBVC period (.1), the OLE period (.2), and the entire study period (.3). For laboratory and vital sign tables ending with ".x," separate tables will be provided for the DBVC period (.1) and the OLE period (.2).

Figures

Figure No.	Title
4.1.1	Proportion of Participants Achieving WI-NRS4 in the DBVC Period With Nonresponder Imputation
4.1.1.2	Proportion of Participants Achieving WI-NRS4 From Baseline to Week 52
4.1.1.3	Forest Plot of the Differences in WI-NRS4 Response Rates at Week 12
4.1.2.1	Proportion of Participants Achieving WI-NRS4 From Day 1 to Day 7 With Multiple Imputation
4.1.2.2	Proportion of Participants Achieving WI-NRS4 From Day 1 to Day 14
4.1.3.1	Mean and Standard Error Plot of By-Visit WI-NRS Score in the DBVC Period
4.1.3.2	Mean and Standard Error Plot of Change From Baseline in By-Visit WI-NRS Score in the DBVC Period
4.1.4	Kaplan-Meier Curve of the Time to ≥ 2-Point Improvement in WI-NRS Score in the DBVC Period
4.1.5	Kaplan-Meier Curve of the Time to ≥ 4-Point Improvement in WI-NRS Score in the DBVC Period
4.1.6.1	Mean and Standard Error Plot of Daily WI-NRS Score From Baseline to Day 14
4.1.6.1	Mean and Standard Error Plot of Change From Baseline in Daily WI-NRS Score From Day 1 to Day 14
4.2.1	Proportion of Participants Achieving Overall-TS in the DBVC Period With Nonresponder Imputation
4.2.2	Proportion of Participants Achieving Overall-TS From Baseline to Week 52
4.3.1	Proportion of Participants Achieving IGA-CPG-S-TS in the DBVC Period With Nonresponder Imputation
4.3.2	Proportion of Participants Achieving IGA-CPG-S-TS From Baseline to Week 52
4.4.1	Proportion of Participants Achieving IGA-CPG-A-TS in the DBVC Period
4.5.1	Mean and Standard Error Plot of By-Visit Skin Pain NRS Score in the DBVC Period
4.5.2	Mean and Standard Error Plot of Change From Baseline in By-Visit Skin Pain NRS Score in the DBVC Period
4.6.1	Proportion of Participants Achieving > 75% Healed Lesions From PAS in the DBVC Period
4.7.1.1	Mean and Standard Error Plot of DLQI Total and Subscale Scores in the DBVC Period
4.7.1.2	Mean and Standard Error Plot of Change From Baseline in DLQI Total and Subscale Scores in the DBVC Period
4.7.2	Proportion of Participants Achieving ≥ 4-Point Improvement in DLQI Total Score in the DBVC Period
4.8.1	Mean and Standard Error Plot of EQ VAS in the DBVC Period
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[redacted]	

Figure No.	Title
[redacted]	
4.16.1	Box Plot of Selected Laboratory Values in the DBVC Period
4.16.2	Box Plot of Change From Baseline in Selected Laboratory Values During the DBVC Period
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Listings

Listing No.	Title
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2.2.2	Protocol Deviations
2.3	Analysis Populations
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2.4.2	Baseline Disease Characteristics
2.4.3	Disease History
2.4.4	Medical History
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2.6.2	Overall-TS
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2.6.5.2	Daily Skin Pain NRS Score
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[redacted]	

Listing No.	Title
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2.7.3	Serious Adverse Events
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