Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of Povorcitinib in Participants with Prurigo Nodularis

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Statistical Analysis Plan

INCB 54707-206

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of Povorcitinib in Participants with Prurigo Nodularis

IND Number:	**137,156**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
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SAP Author:	[redacted]
Date of Plan:	**15 JUN 2023**

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

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
bpm	beats per minute
$C_{avg,ss}$	average concentration of study drug at steady state
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CRF	case report form
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
[redacted]	[redacted]
Ext-Ev	Extension Evaluable
[redacted]	[redacted]
H1; H2	null hypothesis; alternate hypothesis
[redacted]	[redacted]
HDL	high-density lipoprotein
ICF	informed consent form
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment Treatment Success
ITT	intent-to-treat
[redacted]	[redacted]
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NRI	nonresponder imputation
NRS	numerical rating scale

Abbreviations and Special Terms	Definition
[redacted]	[redacted]
PC	placebo-controlled
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PN	prurigo nodularis
[redacted]	[redacted]
PT	preferred term
[redacted]	[redacted]
QALYs	quality-adjusted life years
QD	once daily
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
SAP	Statistical Analysis Plan
SAE	serious adverse event
SI	International System of Units
SMA	smooth moving average
SOC	system organ class
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
ULN	upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]
WHO	World Health Organization
[redacted]	[redacted]

1. INTRODUCTION

This is a Phase 2, multicenter, randomized, parallel-group, placebo-controlled, double-blind, dose-ranging study to evaluate the efficacy and safety of povorcitinib (15, 45, and 75 mg QD) in participants with PN over a 16-week treatment period, followed by a 24-week single-blind extension period ([redacted] or [redacted] QD). Each participant's dose of povorcitinib in the extension period will be based on their efficacy response (Itch NRS and IGA) at Week 16. A safety follow-up visit will be conducted approximately 4 weeks after the last dose of study drug.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 54707-206 Protocol.

[redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 54707-206 Protocol Amendment 2 dated 06 MAY 2022 and CRFs approved 13 MAR 2023. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol Amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of povorcitinib in PN.	Proportion of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16.
Secondary	
To further assess the treatment effects of povorcitinib.	• Proportion of participants achieving IGA-TS (IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline) at Week 16. • Time to ≥ 4-point improvement from baseline in Itch NRS score.
To evaluate the safety and tolerability of povorcitinib.	The type, frequency, and severity of AEs, including the results of physical examinations, and evaluation of vital signs, ECGs, and laboratory data.
[redacted]	

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. STUDY DESIGN

This is a Phase 2, multicenter, randomized, parallel-group, placebo-controlled, double-blind, dose-ranging study to evaluate the efficacy and safety of povorcitinib (15, 45, and 75 mg QD) over a 16-week double-blind PC period followed by a 24-week single-blind extension period ([redacted] or [redacted] QD). The study will enroll approximately 140 men and women aged 18 to [redacted] years who have had a clinical diagnosis of PN for at least 3 months, received prior treatment for PN, and have a total of ≥ 20 pruriginous lesions in ≥ 2 different body regions, an IGA score ≥ 3, and an Itch NRS score ≥ 5.

Participants will be screened for up to 28 days before the first dose of study drug. On Day 1, eligible participants will be equally randomized to 1 of 4 treatment groups (ie, povorcitinib 15, 45, or 75 mg QD or placebo) and stratified by IGA score (3 vs 4).

The use of rescue medications should be delayed, if possible, for at least 8 weeks after the first dose of study drug; however, the use of rescue medications is allowable at any time during the study in participants who have substantial worsening of PN from baseline (as determined by the investigator). Rescue therapy should be provided commensurate with symptom severity. Participants receiving a prohibited medication as rescue therapy must be withdrawn from study drug.

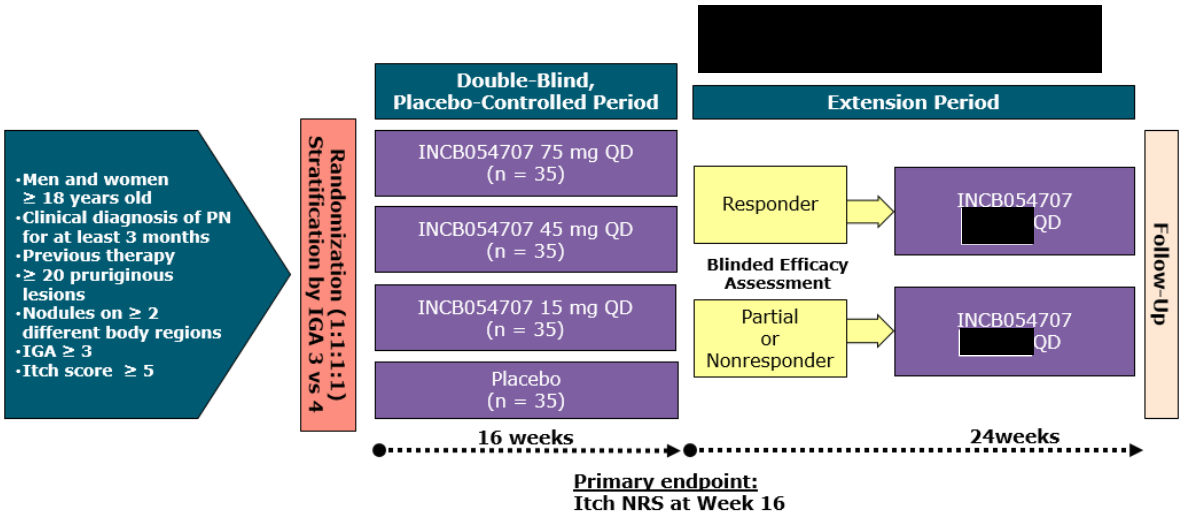
Based on individual IGA and Itch NRS responses at Week 16, participants will receive either povorcitinib [redacted] or [redacted] QD for an additional 24 weeks (extension period). The investigator will know the dose administered during the extension period; however, the participant will remain blinded to the dose they receive. For the extension period, participants will be grouped based on the outcome from the PC period:

- [redacted]
- [redacted]

After the last dose of study drug, participants will be followed for safety. A safety visit will occur at least 28 days following the last dose of study drug.

Figure 1 depicts the study schema.

Figure 1: Study Design Schema



The primary analysis will occur after the primary database lock, when all participants have completed or discontinued from the PC, double-blind treatment period. The sponsor will be unblinded at the time of primary analysis.

The final analysis will occur when all participants have completed or withdrawn from the study.

3.1. Randomization

Approximately 140 participants will be randomized 1:1:1:1 (ie, placebo or povorcitinib 15, 45, or 75 mg) with approximately 35 participants per group.

Participant randomization will be stratified based on IGA score on Day 1 (3 vs 4).

3.2. Control of Type I Error

The overall significance level for efficacy analysis will be 0.05 for 2-sided tests.

A set of hypotheses corresponding to the treatment comparisons between povorcitinib 15, 45, or 75 mg and placebo will be tested in fixed sequential:

- H1: Povorcitinib 75 mg is not equal to placebo in achieving ≥ 4-point improvement in Itch NRS score at Week 16
- H2: Povorcitinib 45 mg is not equal to placebo in achieving ≥ 4-point improvement in Itch NRS score at Week 16
- H3: Povorcitinib 15 mg is not equal to placebo in achieving ≥ 4-point improvement in Itch NRS score at Week 16

Hypothesis 2 will only be tested if H1 is rejected; testing for H3 will be implemented only if H1 and H2 are rejected.

3.3. Sample Size Considerations

In order to provide a safety database and adequate power for efficacy analysis, the total sample size for the study is 140 participants randomized in a 1:1:1:1 ratio to povorcitinib 15, 45, or 75 mg or placebo groups and stratified by IGA score on Day 1 (3 vs 4). The sample size calculation is based on Fisher's exact test for the statistical comparison on the primary efficacy endpoint, ie, the proportion of participants achieving ≥ 4-point improvement in Itch NRS at Week 16. Based on the results from a Phase 2 trial of nemolizumab (Stander et al 2020), the response rate is assumed to be 50% for the povorcitinib 45 and 75 mg groups and 15% for the placebo group. Using a 2-sided alpha of 0.05, 35 participants per group will have 85% power to detect such a difference between either one of the 3 active treatment groups and the placebo group.

3.4. Schedule of Assessments

Refer to Protocol Amendment 2 dated 06 MAY 2022 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study drug (povorcitinib) or placebo is administered to participants. The treatment groups are described in Table 2 for each period, as well as in Section 5.2.

Table 2: Definition of Day 1

Treatment Period	Treatment Group	Day 1
PC period (Up to Week 16)	Placebo Povorcitinib 15 mg Povorcitinib 45 mg Povorcitinib 75 mg	The day of the first dose of study drug (povorcitinib or placebo) administered to participants in the PC period.
Extension period (Week 16 through Week 40)	Week 16 responder: Placebo to povorcitinib [redacted] mg Povorcitinib 15 to [redacted] Povorcitinib [redacted] Povorcitinib [redacted] to [redacted] Week 16 nonresponder: Placebo to povorcitinib [redacted] Povorcitinib 15 to [redacted] Povorcitinib [redacted] o [redacted] Povorcitinib [redacted]	The day of the first dose of study drug (povorcitinib [redacted] or [redacted] mg) administered to participants in the extension period.
Overall period (Up to Week 40)	Povorcitinib 45 mg Povorcitinib 75 mg Note: These groups consist of participants who took only povorcitinib 45 or 75 mg during the study.	The day of the first dose of study drug (povorcitinib 45 or 75 mg) administered to participants in the PC period.

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

4.1.2. Study Day

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

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

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

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

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

4.1.3. Baseline Value

For efficacy and safety evaluations in the PC period, baseline is the last nonmissing measurement obtained before or on the first administration of povorcitinib or placebo in the PC period.

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

Note that for participants who entered the extension period, baseline is defined as follows:

- For efficacy evaluation in the extension period, baseline is the last nonmissing measurement obtained before the first administration of povorcitinib or placebo in the PC period (hereafter referred to as PC baseline).
- For safety evaluation in the extension period, baseline is the last nonmissing measurement obtained before the first administration of study drug in the extension period (hereafter referred to as extension baseline).

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

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

Table 3 provides an outline of baseline definitions for efficacy and safety evaluation in each period.

Table 3: Definitions of Baseline

Treatment Period	Treatment Group	For Efficacy Evaluation	For Safety Evaluation
PC period (Up to Week 16)	Placebo Povorcitinib 15 mg Povorcitinib 45 mg Povorcitinib 75 mg	PC baseline	PC baseline
Extension period (Week 16 through Week 40)	Week 16 responder: Placebo to povorcitinib [redacted] Povorcitinib 15 to [redacted] Povorcitinib [redacted] Povorcitinib [redacted] to [redacted] Week 16 nonresponder: Placebo to povorcitinib [redacted] Povorcitinib 15 to [redacted] Povorcitinib [redacted] o [redacted] Povorcitinib [redacted]	PC baseline	Extension baseline

Table 3: Definitions of Baseline (Continued)

Treatment Period	Treatment Group	For Efficacy Evaluation	For Safety Evaluation
Overall period (Up to Week 40)	Povorcitinib 45 mg Povorcitinib 75 mg Note: These groups consist of participants who took only povorcitinib 45 or 75 mg during the study.	Not applicable	PC 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.

When calculating the time since diagnosis of PN, 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 dose in a specific period is used in deriving variables, such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

4.2. Variable Definitions

The following variable will only be calculated if not reported on the eCRF.

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

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

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of povorcitinib or placebo in the PC period.

For the PC period, concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of povorcitinib or placebo in the PC period and is ongoing or ends on/after the date of first study drug administration in the PC period, OR
- On/after the date of first administration of povorcitinib or placebo in the PC period, and before the date of first administration of povorcitinib in the extension period for participants who enter the extension period.

For the extension period, concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of povorcitinib in the extension period and is ongoing throughout the study or ends on/after the date of first study drug administration in the extension period, OR
- On/after the date of first administration of povorcitinib in the extension period.

For the overall period, concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of povorcitinib in the PC period and is ongoing throughout the study or ends on/after the date of first study drug administration in the PC period, OR
- On/after the date of first administration of povorcitinib in the PC period.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of povorcitinib or placebo in the PC period. 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; v9.1 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, double-blind, placebo-controlled, dose-ranging study followed by a single-blind extension period. Table summaries, unless otherwise indicated, will present data by treatment group. The results will be summarized and presented separately for the PC period, the extension period, and overall period (for safety only) unless otherwise specified.

For the PC period, the treatment groups will be placebo and povorcitinib 15, 45, and 75 mg.

For the extension period, participants will be grouped into 2 cohorts (Week 16 responders and Week 16 nonresponders); these 2 cohorts will then be separated into the following subgroups, per the treatments they received during the PC and extension periods:

- Week 16 responders:
  - Placebo to povorcitinib [redacted]
  - Povorcitinib 15 to [redacted]
  - Povorcitinib [redacted]
  - Povorcitinib [redacted] to [redacted]
- Week 16 nonresponders:
  - Placebo to povorcitinib [redacted]
  - Povorcitinib 15 to [redacted]
  - Povorcitinib [redacted] to [redacted]
  - Povorcitinib [redacted]

Safety results will be summarized and presented by the following treatment groups who took same dose across study:

- Povorcitinib 45 mg will consist of participants who took only 45 mg during the overall period (including participants who received at least 1 dose of [redacted] during both the PC and extension periods, and participants who received at least 1 dose of 45 mg during the PC period and discontinued during the PC period).
- Povorcitinib 75 mg will consist of participants who took only 75 mg during the overall period (including participants who received at least 1 dose of [redacted] during both the PC and extension periods, and participants who received at least 1 dose of 75 mg during the PC period and discontinued during the PC period).

5.3. Analysis Populations

5.3.1. All-Randomized Population

The all-randomized population will include all participants who were randomly assigned to receive placebo or povorcitinib.

5.3.2. Intent-to-Treat Population

All participants who were 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 treatment the participant might apply during their participation in the PC period.

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

5.3.3. Safety Population

The safety population will include all participants who received at least 1 dose of povorcitinib or placebo during the PC period. Treatment groups for this population will be determined according to the actual treatment the participant receives on Day 1 in the PC period regardless of assigned study drug treatment.

All safety analyses for the PC period and the overall period will be conducted using the safety population.

5.3.4. Extension Evaluable Population

All analyses for the extension period will be conducted with the extension evaluable population, which includes all participants who received at least 1 dose of povorcitinib during the extension 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

The demographics, baseline characteristics, and disease history will be summarized by treatment groups and overall.

6.1.1. Demographics and Baseline Characteristics

The following demographics will be summarized for the ITT and the extension evaluable populations: age; age group (< 65 and ≥ 65 years); sex; race; ethnicity; weight; height; BMI; and BMI category (< 25 kg/m^2, ≥ 25 to < 30 kg/m^2, ≥ 30 to < 40 kg/m^2, ≥ 40 to < 50 kg/m^2, and ≥ 50 kg/m^2).

The following demographic will be summarized for the ITT population only: tobacco use (never used, current user, or former user).

6.1.2. Baseline Disease Characteristics and Disease History

The following baseline disease characteristics and disease history will be summarized for all participants in the ITT population, including, but not limited to:

- Disease duration (years)
- Fitzpatrick scale skin type (Type I/II/III/IV/V/VI)
- PN family history
- Prior therapy for PN (yes/no)
- Prior therapeutic response (complete, good, limited improvement, lack of efficacy)
- Selected comorbidities
- [redacted]
- Baseline IGA score
- Baseline Itch NRS score (See Section 7.2.4.1)
- [redacted]

Note: Disease duration (years) will be calculated as follows:

Disease duration (years) = (date of randomization – date of initial PN diagnosis + 1) / 365.25.

6.1.3. Medical History

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

6.2. Disposition of Participant

The number of participants enrolled by country and/or site will be provided by treatment group and overall.

The following categories will be summarized by treatment group and overall for the ITT population in the PC period:

- Number (%) of participants who were randomized
- Number (%) of participants who were treated in the double-blind PC period
- Number (%) of participants who completed treatment in the PC period through Week 16
- Number (%) of participants who discontinued treatment with a primary reason for discontinuation in the PC period
- Number (%) of participants who withdrew from the study with a primary reason for withdrawal in the PC period
- Number (%) of participants who withdrew from study due to COVID-19 in the PC period

The following categories will be summarized by treatment group and overall for the extension evaluable population in the extension period:

- Number (%) of participants who were treated in the extension period
- Number (%) of participants who completed treatment in the extension period
- Number (%) of participants who discontinued the study treatment with a primary reason for discontinuation in the extension period
- Number (%) of participants who completed the study
- Number (%) of participants who withdrew from the study with a primary reason for withdrawal in the extension period
- Number (%) of participants who withdrew from study due to COVID-19 in the extension period

6.3. Protocol Deviations

Protocol deviations recorded will be summarized and listed for the ITT and extension evaluable populations, as well as the individual protocol deviations indicated on the eCRF.

6.4. Exposure

For participants in the safety population in the PC period and the extension evaluable population in the extension period, as well as for participants who only took povorcitinib 45 or 75 mg during the overall period, the exposure to the study drug will be descriptively summarized by treatment group as follows:

- **Duration of treatment with povorcitinib (days)**: Date of last dose of study drug in the specific period – date of first dose of study drug in the specific period + 1.

Note that the date of first and last dose of the study drug in each period are defined in Table 4.

Table 4: Definition of First and Last Dose Date

Treatment Period	Treatment Group	First Dose Date	Last Dose Date
PC period	Placebo Povorcitinib 15 mg Povorcitinib 45 mg Povorcitinib 75 mg	Date of first dose of study drug administration in the PC period	Date of last dose of study drug administration in the PC period
Extension period	Week 16 responders: Placebo to povorcitinib [redacted] Povorcitinib 15 to [redacted] Povorcitinib [redacted] Povorcitinib [redacted]o [redacted] Week 16 nonresponders: Placebo to povorcitinib [redacted] Povorcitinib 15 to [redacted] Povorcitinib [redacted]o [redacted] Povorcitinib [redacted]	Date of first dose of study drug administration in the extension period	Date of last dose of study drug administration in the extension period
Overall period	Povorcitinib 45 mg Povorcitinib 75 mg Note: These groups consist of participants who took only povorcitinib 45 or 75 mg during the study.	Date of first dose of study drug administration in the PC period	Date of first dose of study drug administration during the overall period

For participants in the safety population in the PC period and the extension evaluable population in the extension period, the average daily dose of povorcitinib and total actual dose of povorcitinib administered will be summarized by treatment groups as follows:

- **Average daily dose of povorcitinib (mg/day)**: Total actual povorcitinib dose taken in the specific period (mg) / [duration of treatment with povorcitinib in the specific period (days) – number of interrupted days with povorcitinib in the specific period].
- **Total actual dose of povorcitinib administered (mg)**: (Total number of tablets dispensed in the specific period – total number of tablets returned in the specific period) × 15 (mg/tablet) × p_T,

  where p_T denotes the proportion of povorcitinib among the 5 tablets taken daily (ie, $p_T = 0$ (0/5) for placebo group, 1/5 for povorcitinib 15 mg group, 3/5 for povorcitinib 45 mg group, and 5/5 for povorcitinib 75 mg group).

The total number of tablets dispensed and returned in each period is based on information entered on the Drug Accountability eCRF. Should the dispensed drug not be returned, the actual dose taken, starting from the dispense date of the unreturned drug, will be imputed by the dose taken per the Compliance eCRF.

6.5. Study Drug Compliance

For participants in the safety and the extension evaluable populations, the overall compliance (%) for povorcitinib/placebo will be calculated as follows:

Compliance (%) = 100 × [total dose actually taken in the specific period] / [total prescribed dose in the specific period].

The total prescribed dose in the specific period is defined as the sum of the doses prescribed by the investigator accounting for dose interruptions during the specific period; this will be calculated as follows:

[Duration of treatment with study drug in the specific period – number of days with dose interruptions in the specific period] × 5 (tablets/day).

The total actual dose taken in a specific period will be calculated as follows:

Total number of tablets dispensed in the specific period – total number of tablets returned in the specific period.

For more details on the total number of tablets dispensed and returned, see Section 6.4.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. For the ITT population in the PC period, both prior and concomitant medication will be summarized by treatment group and overall. For the extension evaluable population in the extension period, only concomitant medications will be summarized by treatment group and overall. For participants who took only povorcitinib 45 or 75 mg during the overall period, concomitant medications will be summarized by treatment group and overall. The number and percentage of participants in all populations will be summarized by WHO drug class and WHO drug preferred term.

7. EFFICACY

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

7.1. General Considerations

All by-visit analyses for the extension evaluable population will include the follow-up period, if the data are available or unless otherwise specified. Likewise, unless otherwise stated, the strata identified in the randomization process will be used in all efficacy analyses.

7.2. Efficacy Parameters

7.2.1. Investigator's Global Assessment

The IGA for chronic prurigo considers the number of pruriginous lesions, which includes papules, nodules, plaques, umbilicated ulcers and ulcers to rate the overall severity on a scale of 0 to 4 (Zeidler et al 2021; see Table 5). The nodular rating will be performed at scheduled visits.

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

Table 5: Investigator's Global Assessment

Grade	Severity	Description
0	Clear	No nodules (0 nodules)
1	Almost clear	Rare palpable pruriginous nodules (approximately 1-5 nodules)
2	Mild	Few palpable pruriginous nodules (approximately 6-19 nodules)
3	Moderate	Many palpable pruriginous nodules (approximately 20-100 nodules)
4	Severe	Abundant palpable pruriginous nodules (over 100 nodules)

[redacted]

[redacted]

7.2.4. Patient-Reported Outcomes

Patient-reported outcomes and quality of life will be assessed using the following tools:

- Itch NRS (see Section 7.2.4.1)
- [redacted]

7.2.4.1. Itch Numerical Rating Scale

Each evening, participants will assess their worst level of itch during the past 24 hours on a scale of 0 (no itch) to 10 (worst itch imaginable) via a handheld device (eDiary).

The baseline Itch NRS score will be determined by averaging the 7 daily Itch NRS scores before Day 1 (ie, Day −7 to Day −1). Should ≥ 4 of the 7 days of the daily Itch NRS scores be missing prior to Day 1, then the baseline Itch NRS will be set to "missing."

The by-visit Itch NRS score for postbaseline visits will be determined by averaging the 7 daily Itch NRS scores before the visit day. If 4 or more daily Itch NRS scores out of the 7 days before the visit day are missing, the Itch NRS at the visit will be set to missing.

The most appropriate threshold for defining a clinically relevant, in-person response is ≥ 4-point reduction relative to baseline (Kimball et al 2016).

For time to ≥ 4-point improvement from baseline in Itch NRS score, 3-day smooth moving average (SMA) method will be used. For each Day X (X = 2 to two days before the first dose date in extension period for participants who entered extension period, or one day before discontinuation date for participants who discontinued PC period), a SMA value is calculated as the average of daily Itch NRS scores on Day X − 1, Day X, and Day X + 1. If 1 or more daily Itch NRS scores out of the 3-day interval are missing, the SMA value for the day will be set to missing. The first day achieving ≥ 4-point improvement from baseline in daily Itch NRS score is defined as the day with both the value at the day, and its SMA value are ≥ 4-point lower as compared to the baseline Itch NRS score defined above. Then the time to ≥ 4-point improvement from baseline in Itch NRS score will be calculated as:

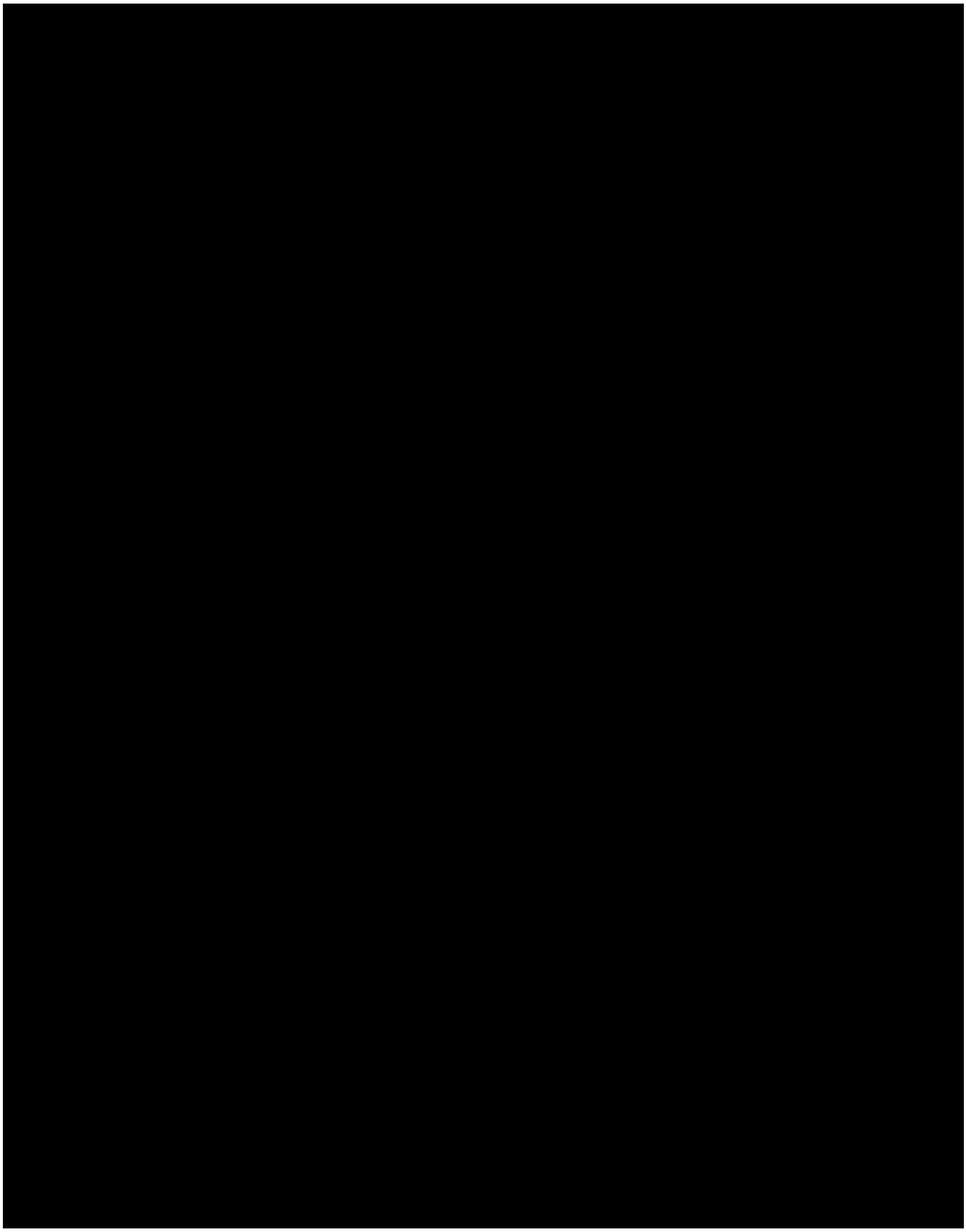
(Date of first day achieving ≥ 4-point improvement from baseline in daily Itch NRS score – Day 1 date +1).

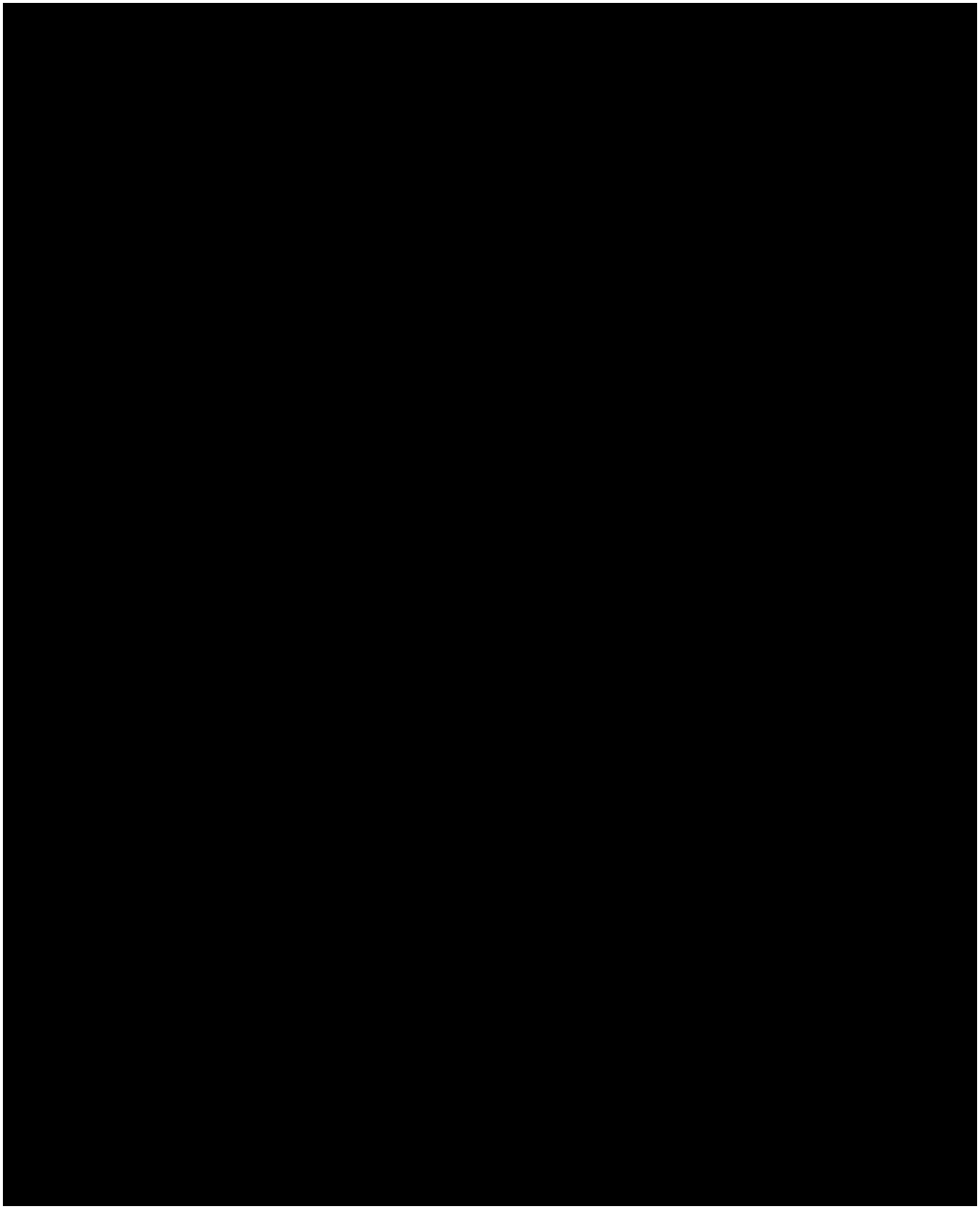
Participants who did not achieve ≥ 4-point improvement from baseline in Itch NRS score during the PC period will be censored as follows:

- Participants who completed the PC treatment period through Week 16 without having the event will be censored at one day before the first dose date in extension period, and the censored time will be calculated as: (Date of one day before the first dose date in extension period – Day 1 date +1)
- Participants who discontinued during the PC period without having the event will be censored at the date of discontinuation in PC period, and the censored time will be calculated as: (Date of discontinuation in PC period – Day 1 date +1).

[redacted]

[redacted]





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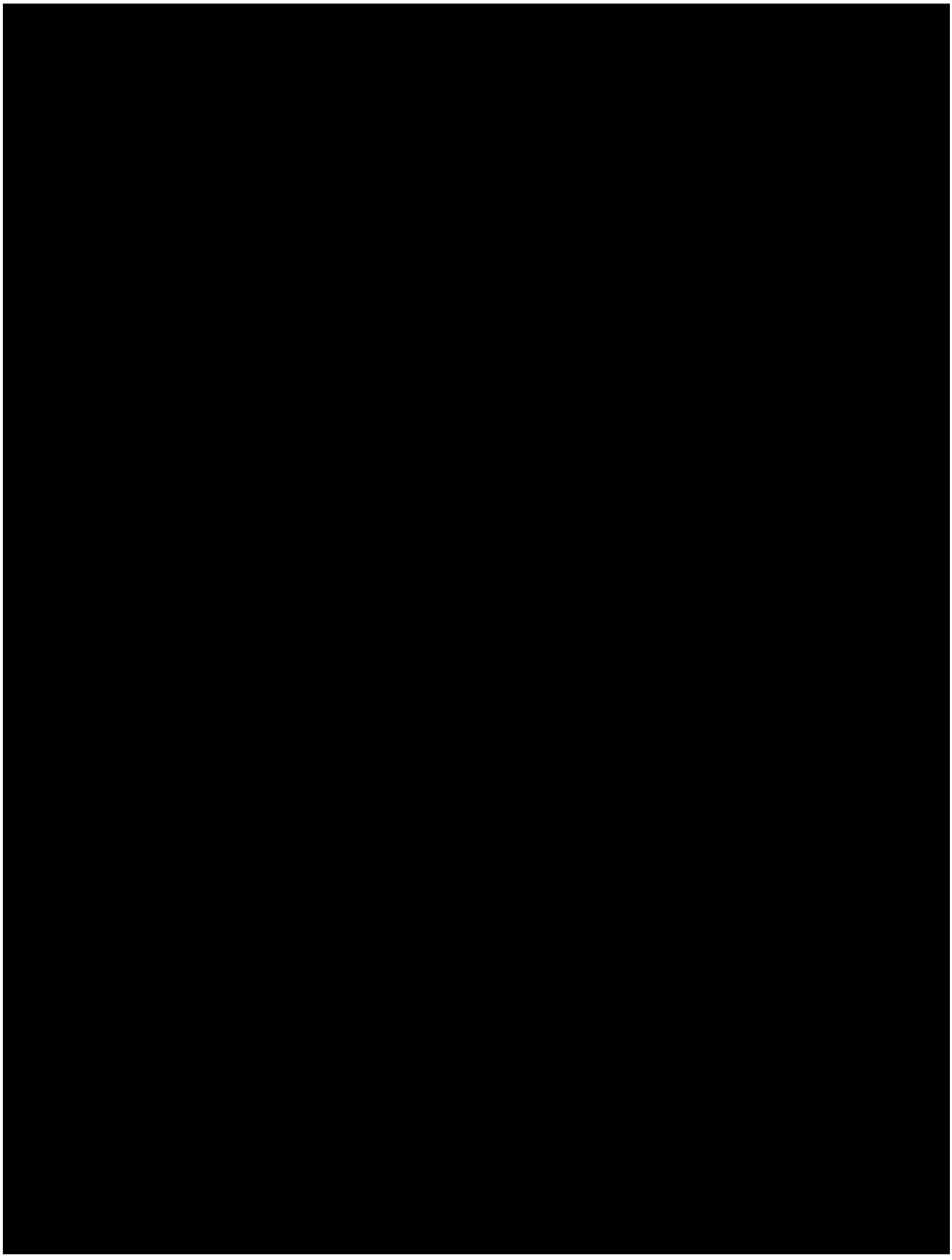

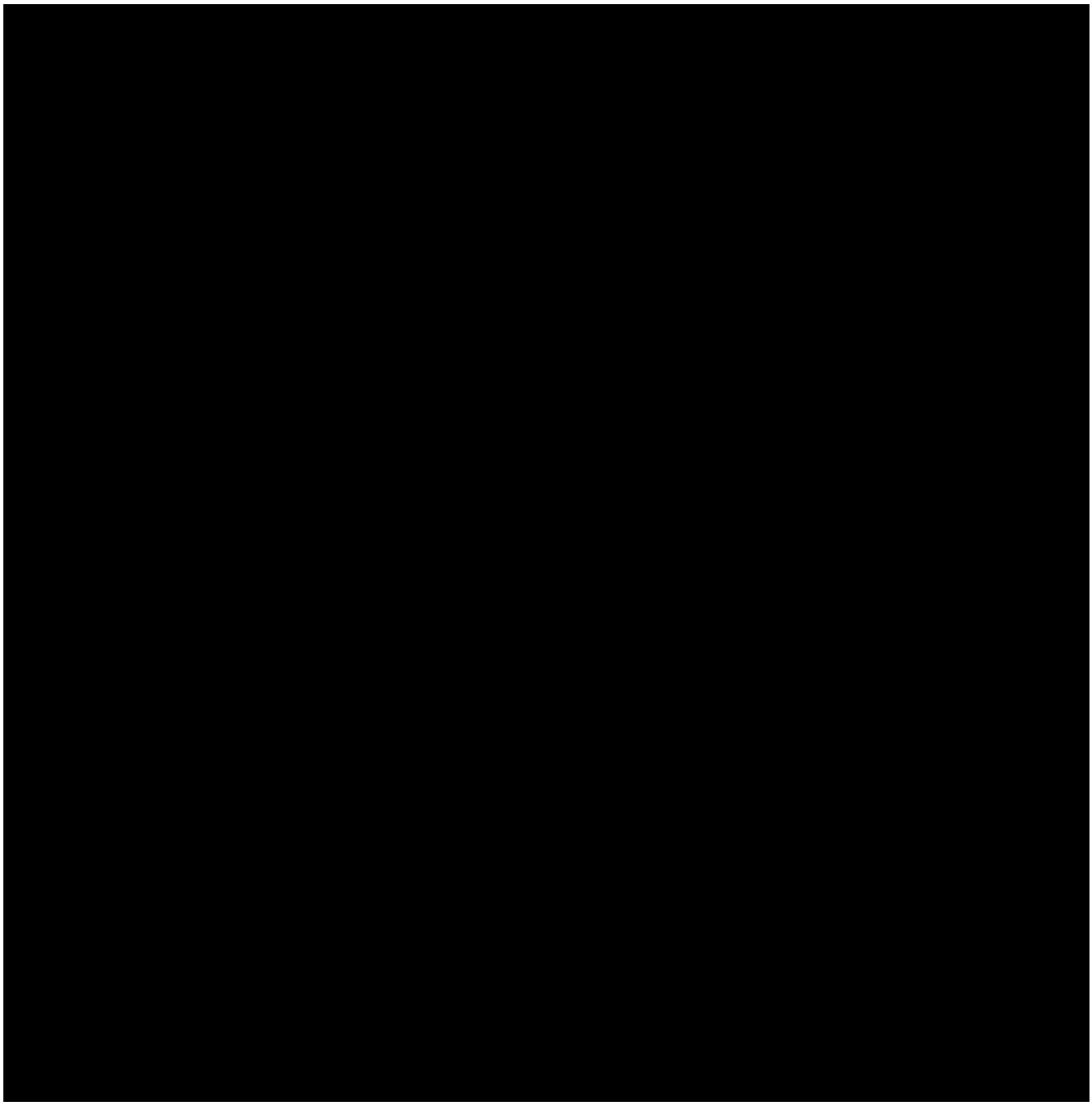

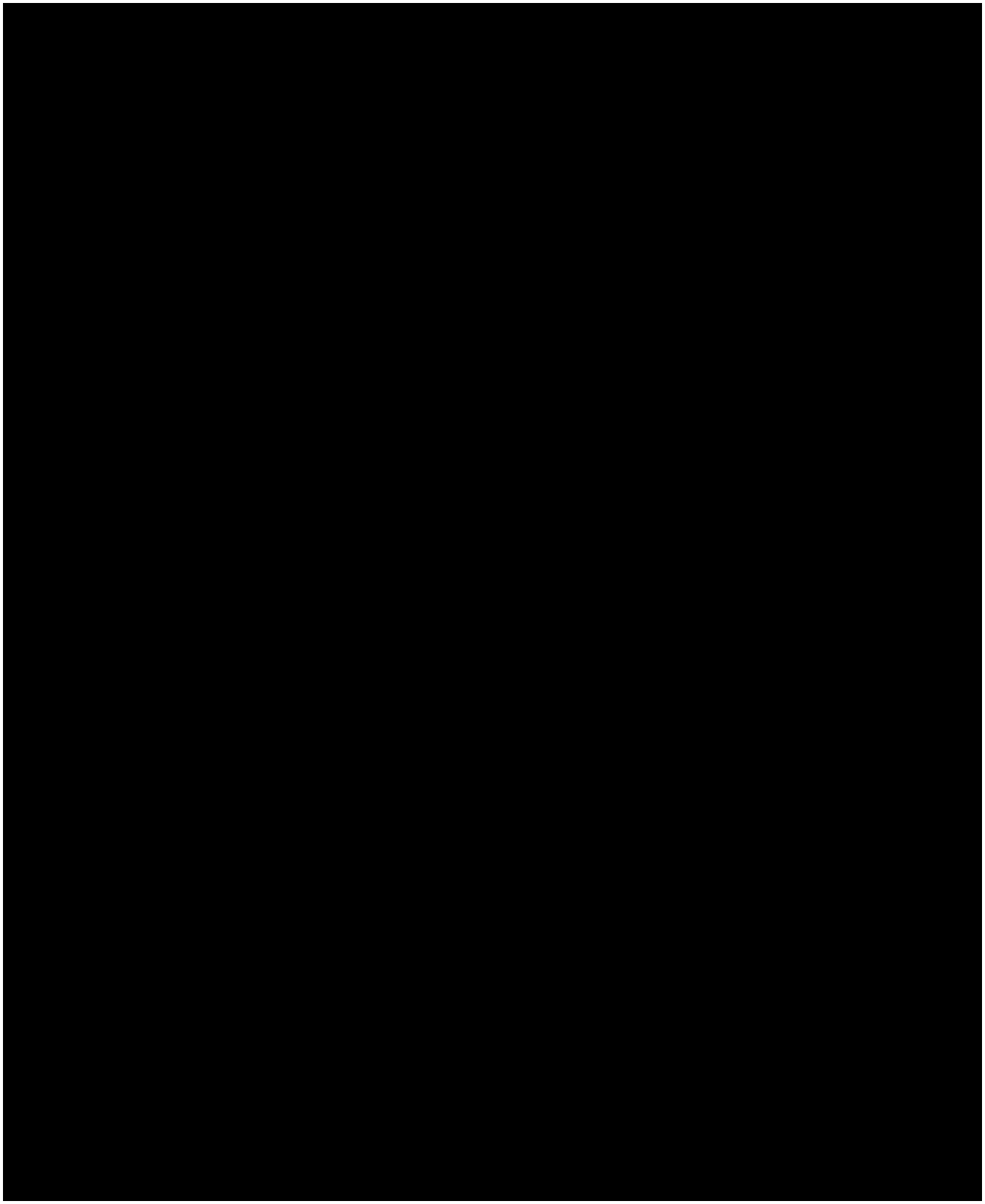

7.3. Efficacy Hypotheses

The primary hypothesis is that povorcitinib 75 mg is superior to placebo in proportion of participants achieving ≥ 4-point improvement in Itch NRS at Week 16. If the response rates of achieving ≥ 4-point improvement in Itch NRS at Week 16 in the povorcitinib 75 mg and placebo groups are denoted as p_T and p_C, respectively, then the primary hypotheses of the study are as follows:

- H_0 (null hypothesis): $p_T = p_C$
- H_A (alternative hypothesis): $p_T \neq p_C$

7.4. Analysis of the Primary Efficacy Parameter

The primary efficacy endpoint is the proportion of participants achieving ≥ 4-point improvement in Itch NRS at Week 16.

7.4.1. Primary Efficacy Analysis

The primary efficacy analysis will compare povorcitinib 75 mg versus placebo in the proportion of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16 using an exact logistic regression (Mehta and Patel 1995) based on the ITT population. This model will include the treatment groups (placebo and povorcitinib 15, 45, and 75 mg) and stratification factor (Day 1 IGA score [3 or 4]). The unadjusted p-values between each of the povorcitinib groups and the placebo group will be compared at 2-sided α = 0.05 in a fixed sequence from high dose to low dose (75 mg vs placebo → 45 mg vs placebo → 15 mg vs placebo); the lower dose will be tested only if the null hypothesis associated with the higher dose is rejected. The estimated odds ratios and corresponding 95% CIs will be provided as well. All observed nonresponders, as well as all participants who discontinue study treatment, withdraw from the study for any reason at any time before the timepoint of interest (ie, Week 16), or those participants that do not have the postbaseline assessment at the timepoint of interest, will be defined as nonresponders for the NRI analysis. All participants who receive rescue therapy during the placebo-controlled period will be imputed as nonresponders for all subsequent visits after the initiation date of rescue therapy.

The number of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16 and the respective rates, as well as the 2-sided 95% exact CIs, which are based on the Clopper-Pearson method, will be presented by treatment group.

7.4.2. 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:

- Age group (< 65 and ≥ 65 years)
- Gender (male, female)
- Geographical region
- Baseline IGA (3 vs 4)

The primary efficacy endpoint will be summarized using descriptive statistics based on the ITT population for the aforementioned subgroups.

7.4.3. Sensitivity and Supportive Analyses for Primary Endpoint

Not applicable.

7.5. Analysis of the Secondary Efficacy Parameters

The secondary efficacy endpoints include the proportion of participants achieving IGA-TS at Week 16 and the time it takes to achieve a ≥ 4-point improvement from baseline in the Itch NRS score.

The proportion of participants achieving IGA-TS at Week 16 will be summarized using descriptive statistics. The NRI approach will be used to address initiation of rescue medication, treatment discontinuation, and missing data.

For the time to ≥ 4-point improvement from baseline in Itch NRS score during the PC period, Kaplan-Meier curves will be presented by treatment groups. The number of participants, number of events, and number of censoring events will be summarized by treatment groups. The Kaplan-Meier estimate of median time will be presented with its 95% CI. The 95% CI will be calculated using the method by Brookmeyer and Crowley (1982).

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 PC period, the extension evaluable population in the extension period, and for participants who took only povorcitinib 45 or 75 mg during the overall period, 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 the first dose of study drug and up to 30 days after the last dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

A TEAE in the PC period is any AE with a start time after the first dose of study drug in the PC period and until the end of the safety follow-up, or prior to the first dose in the extension period for participants who entered in to the extension period.

A TEAE in the extension period is any AE with a start time after the first dose of study drug in the extension period and until the end of the safety follow-up.

For participants who took only povorcitinib 45 or 75 mg during overall period, a TEAE is any AE with a start time after the first dose of study drug in the PC period and until the end of the safety follow-up.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the National Cancer Institute 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 drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, 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.

9.2.2. Adverse Event Summaries

Adverse events will be summarized by treatment group and povorcitinib dose groups combined for the safety population in the PC period, and by treatment group and overall in each cohort (ie, Week 16 responders and nonresponders) for the extension evaluable population in the extension period, and by treatment group and overall for participants who took only povorcitinib 45 or 75 mg during the overall period.

An overall summary of AEs 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 a fatal TEAE
- Number (%) of participants who had TEAE requiring concomitant medication

The following summaries will be produced by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- 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 with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs leading to dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of study drug by MedDRA SOC and PT
- Summary of TEAEs requiring concomitant medications by MedDRA SOC and PT

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

Laboratory values, change from baseline values, and percent change from baseline values will be summarized descriptively by visit, and non-numeric test values will be tabulated when necessary. Baseline will be determined according to Section 4.1.3. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

9.3.2. Laboratory Value Summaries

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, 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. In addition, boxplots will be provided for creatine kinase, hemoglobin, hematocrit, platelet count, high sensitivity C-reactive protein, lymphocyte absolute count, neutrophil absolute count, white blood cell count, total cholesterol, HDL, LDL, and HDL/LDL ratio.

For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary will be produced for each test. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, 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. 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 experienced worsening of laboratory abnormalities will be summarized by maximum severity.

9.3.3. Potentially Clinically Important Laboratory Values

Criteria for potentially clinically important laboratory values are listed in Table 6. The number and percentage of participants with postbaseline laboratory values that meet each criterion will be summarized at each scheduled visit by treatment group. Participants with potentially clinically important laboratory values will also be listed.

Table 6: Criteria for Potentially Clinically Important Laboratory Values

Laboratory Parameter	Grade (Criteria)
Hemoglobin	Grade 2 (80 to < 100 g/L) Grade 3 (< 80 g/L)
Lymphocytes	Grade 2 (0.5 to < 0.8 × 10^9/L) Grade 3 (0.2 to < 0.5 × 10^9/L) Grade 4 (< 0.2 × 10^9/L)
Neutrophils	Grade 2 (1.0 to < 1.5 × 10^9/L) Grade 3 (0.5 to < 1.0 × 10^9/L) Grade 4 (< 0.5 × 10^9/L)

Table 6: Criteria for Potentially Clinically Important Laboratory Values (Continued)

Laboratory Parameter	Grade (Criteria)
Platelets	Grade 2 (50 to < 75 × 10^9/L) Grade 3 (25 to < 50 × 10^9/L) Grade 4 (< 25 × 10^9/L)
Creatinine	Grade 2 (> 1.5 to 3 × ULN or > 1.5 to 3 × baseline) Grade 3 (> 3 to 6 × ULN or > 3 × baseline) Grade 4 (> 6 × ULN)
Creatine kinase	Grade 2 (> 2.5 to 5 × ULN) Grade 3 (> 5 to 10 × ULN) Grade 4 (> 10 × ULN)

9.3.4. Potential Drug-Induced Liver Injury Events

According to FDA's guidance on Drug-Induced Liver Injury (2009), the criteria for potential DILI events include the following:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- ALT or AST ≥ 3 × ULN
- ALT or AST ≥ 5 × ULN
- ALT or AST ≥ 10 × ULN
- ALT or AST ≥ 20 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN
- Total bilirubin ≥ 2 × ULN
- ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN

Note that combination of values need to be measured on the same day.

The number and percentage of participants with postbaseline liver specific function test values that meet these criteria will be presented at each scheduled visit by treatment group. Participants with potential DILI events will also be listed.

9.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, temperature, respiratory rate, and weight will be summarized descriptively. Baseline will be determined according to Section 4.1.3.

Normal ranges for vital sign values are defined in Table 7. 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%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 7: Normal Ranges for Vital Sign Values

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	≤ 38ºC	≥ 35.5ºC
Respiratory rate	≤ 24 breaths/min	≥ 8 breaths/min

9.5. Electrocardiograms

Twelve-lead ECGs, including PR, QT, QRS and QTcF intervals, will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of povorcitinib or placebo.

Normal ranges for ECG values are defined in Table 8. The ECG values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT and QTcF values, defined as absolute values > 450 millisecond, > 500 millisecond, or change from baseline > 30 millisecond, will be summarized.

Table 8: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
PR	≤ 220 ms	≥ 75 ms
QT	≤ 500 ms	≥ 300 ms
QRS	≤ 120 ms	≥ 50 ms
QTcF	≤ 450 ms	≥ 295 ms

10. INTERIM ANALYSES

There are no planned, formal interim analyses for this study.

10.1. Overview of Interim Analyses

No formal interim analysis is planned in this study.

10.2. Data Cutoff for Interim Analysis

Not applicable.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 9.

Table 9: Statistical Analysis Plan Versions

SAP Version	Date
Original	03 APR 2023
Amendment 1	15 JUN 2023

11.1. Changes to Protocol-Defined Analyses

Not applicable.

11.2. Changes to the Statistical Analysis Plan

11.2.1. Amendment 1

Updated Section 3 to better align with Section 6.3 of Protocol Amendment 2. In Appendix A, the title of Figure 4.2.2.2 was corrected.

12. REFERENCES

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Food and Drug Administration. Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. 2009.

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Stander S, Yosipovitch G, Legat FJ, et al. Trial of nemolizumab in moderate-to-severe prurigo nodularis. N Engl J Med 2020;382:706-716.

Zeidler C, Pereira MP, Augustin M, Spellman M, Ständer S. Investigator's global assessment of chronic prurigo: a new instrument for use in clinical trials. Acta Derm Venereol 2021;101:1-5.

[redacted]

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 most current Standard Safety Tables. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The list 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
1.1 Baseline and Demographics Characteristics			
1.1.1	Analysis Populations	All	X
1.1.2.x	Summary of Participant Disposition in the PC Period	ITT/Ext-Ev	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	ITT	X
1.1.4.x	Summary of Protocol Deviations in the PC Period	ITT/Ext-Ev	X
1.2 Demographics and Baseline Characteristics			
1.2.x	Summary of Demographics and Baseline Characteristics in the PC Period	ITT/Ext-Ev	X
1.3 Baseline Disease Characteristics			
1.3.1	Summary of Baseline Disease Characteristics	ITT	X
1.4 Prior and Concomitant Medication			
1.4.1	Summary of Prior Medications	ITT	X
1.4.2	Summary of Concomitant Medications in the PC Period	ITT/Ext-Ev	X
1.5 Others			
1.5	Summary of General Medical History	ITT	X
Efficacy			
2.1 Primary Efficacy			
ITCH NRS			
2.1.1	Summary and Analysis of Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit in the PC Period	ITT	
2.1.2	Summary of Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit by Age Group in the PC Period	ITT	
2.1.3	Summary of Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit by Gender in the PC Period	ITT	
2.1.4	Summary of Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit by Baseline IGA (3 v 4) in the PC Period	ITT	
2.1.5	Summary of Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit by Geographical Region in the PC Period	ITT	
2.2 Secondary Efficacy			
2.2.1 IGA-TS			
2.2.1.x	Summary of Proportion of Participants Achieving IGA-TS by Visit in the PC Period	ITT/Ext-Ev	

Table No.	Title	Population	Standard
2.2.2 ITCH NRS			
2.2.2.1	Summary of Time to ≥ 4-Point Improvement From Baseline in Itch NRS Score in the PC Period	ITT	

[redacted]

Table No.	Title	Population	Standard
[redacted]			
Safety			
3.1 Dose Exposure			
3.1.1.x	Summary of Study Drug Exposure in the PC Period	Safety/Ext-Ev	X
3.1.1.3	Summary of Study Drug Exposure for Participants Who Took Only Povorcitinib 45 mg or 75 mg Throughout Study Participation (Overall Period)	Safety	X
3.1.2.x	Summary of Study Drug Compliance in the PC Period	Safety/Ext-Ev	X
3.2 Adverse Events			
3.2.1.x	Overall Summary of Treatment-Emergent Adverse Events in the PC Period	Safety/Ext-Ev	X
3.2.1.3	Overall Summary of Treatment-Emergent Adverse Events for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.2.x	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.3.x	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the PC Period	Safety/Ext-Ev	X
3.2.3.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.4.x	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity in the PC Period	Safety/Ext-Ev	X
3.2.4.3	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X

Table No.	Title	Population	Standard
3.2.5.x	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category in the PC Period	Safety/Ext-Ev	X
3.2.5.3	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.6.x	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.6.3	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	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 in the PC Period	Safety/Ext-Ev	X
3.2.7.3	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.8.x	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.8.3	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.9.x	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the PC Period	Safety/Ext-Ev	X
3.2.9.3	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.10.x	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.10.3	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.11.x	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in the PC Period	Safety/Ext-Ev	X
3.2.11.3	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	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 in the PC Period	Safety/Ext-Ev	X

Table No.	Title	Population	Standard
3.2.12.2	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the Extension Period	Ext-Ev	X
3.2.12.3	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.13.x	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.13.3	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.14.x	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.14.3	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.15.x	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.15.3	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.16.x	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.16.3	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.2.17.x	Summary of Treatment-Emergent Adverse Events Requiring Concomitant Medications by MedDRA System Organ Class and Preferred Term in the PC Period	Safety/Ext-Ev	X
3.2.17.3	Summary of Treatment-Emergent Adverse Events Requiring Concomitant Medications by MedDRA System Organ Class and Preferred Term for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation	Safety	X
3.3 Laboratory			
3.3.1.1.x	Summary of Laboratory Values in the PC Period - Hematology	Safety/Ext-Ev	X
3.3.1.1.3	Summary of Laboratory Values for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation - Hematology	Safety	X
3.3.1.2.x	Summary of Laboratory Values in the PC Period - Chemistry	Safety/Ext-Ev	X
3.3.1.2.3	Summary of Laboratory Values for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation - Chemistry	Safety	X

Table No.	Title	Population	Standard
3.3.1.3.x	Summary of Laboratory Values in the PC Period - Lipid Panel	Safety/Ext-Ev	X
3.3.1.3.3	Summary of Laboratory Values for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation - Lipid Panel	Safety	X
3.3.1.4.x	Summary of Laboratory Values in the PC Period - Urinalysis	Safety/Ext-Ev	X
3.3.1.4.3	Summary of Laboratory Values for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Study Participation - Urinalysis	Safety	X
3.3.1.5.x	Summary of Laboratory Values in the PC Period - Thyroid Function Markers and Inflammation Marker	Safety/Ext-Ev	X
3.3.1.5.3	Summary of Laboratory Values for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Thyroid Function Markers and Inflammation Marker	Safety	X
3.3.2.1.x	Shift Summary of Hematology Laboratory Values - to the Worst Abnormal Value in the PC Period	Safety/Ext-Ev	X
3.3.2.1.3	Shift Summary of Hematology Laboratory Values - to the Worst Abnormal Value for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.3.2.2.x	Shift Summary of Chemistry Laboratory Values - to the Worst Abnormal Value in the PC Period	Safety/Ext-Ev	X
3.3.2.2.3	Shift Summary of Chemistry Laboratory Values - to the Worst Abnormal Value for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.3.2.3.x	Shift Summary of Lipid Panel Laboratory Values - to the Worst Abnormal Value in the PC Period	Safety/Ext-Ev	X
3.3.2.3.3	Shift Summary of Chemistry Laboratory Values - to the Worst Abnormal Value for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.3.3.1.x	Shift Summary of Hematology Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal Value in the PC Period	Safety/Ext-Ev	X
3.3.3.1.3	Shift Summary of Hematology Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.3.3.2.x	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal Value in the PC Period	Safety/Ext-Ev	X
3.3.3.2.3	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.3.3.3.x	Shift Summary of Lipid Panel Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal Value in the PC Period	Safety/Ext-Ev	X
3.3.3.3.3	Shift Summary of Lipid Panel Laboratory Values in CTCAE Grade - to the Worst Grade Abnormal for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.3.4.x	Summary of Potential Clinically Important Laboratory Values by Visit in the PC Period	Safety/Ext-Ev	
3.3.4.3	Summary of Potential Clinically Important Laboratory Values by Visit for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	
3.3.5.x	Summary of Potential Drug Induced Liver Injury Events by Visit in the PC Period	Safety/Ext-Ev	

Table No.	Title	Population	Standard
3.3.5.3	Summary of Potential Drug Induced Liver Injury Events by Visit for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	
3.4 Vital Signs			
3.4.1.x	Summary of Systolic Blood Pressure in the PC Period	Safety/Ext-Ev	X
3.4.1.3	Summary of Systolic Blood Pressure for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.4.2.x	Summary of Diastolic Blood Pressure in the PC Period	Safety/Ext-Ev	X
3.4.2.3	Summary of Diastolic Blood Pressure for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.4.3.x	Summary of Pulse in the PC Period	Safety/Ext-Ev	X
3.4.3.3	Summary of Pulse for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.4.4.x	Summary of Respiratory Rate in the PC Period	Safety/Ext-Ev	X
3.4.4.3	Summary of Respiratory for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.4.5.x	Summary of Body Temperature in the PC Period	Safety/Ext-Ev	X
3.4.5.3	Summary of Body Temperature for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period	Safety	X
3.5 ECG			
3.5.1.1.x	Summary of PR Interval (ms) From 12-Lead ECG by Visit in the PC Period	Safety/Ext-Ev	X
3.5.1.2.x	Summary of QRS Interval (ms) From 12-Lead ECG by Visit in the PC Period	Safety/Ext-Ev	X
3.5.1.3.x	Summary of QT Interval (ms) From 12-Lead ECG by Visit in the PC Period	Safety/Ext-Ev	X
3.5.1.4.x	Summary of QTcF Interval (ms) From 12-Lead ECG by Visit in the PC Period	Safety/Ext-Ev	X
3.5.1.5.x	Summary of Heart Rate (bpm) From 12-Lead ECG by Visit in the PC Period	Safety/Ext-Ev	X
3.5.1.6.x	Summary of Outliers of QT and QTcF Interval Values (ms) From 12-Lead ECG by Visit in the PC Period	Safety/Ext-Ev	X
3.5.1.7.x	Summary of Clinically Significant ECG Abnormality by Visit in the PC Period	Safety/Ext-Ev	X

Figures

Figure No.	Title	Population
4.1 Primary Efficacy		
4.1.1	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit in the PC Period Using Nonresponder Imputation	ITT
4.1.2	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit Using Observed Values	ITT
4.1.3.1	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit by IGA Score (3 or 4) in the PC Period	ITT
4.1.3.2	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit Gender in the PC Period	ITT
4.1.3.3	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit Age Group (< 65, ≥ 65 years) in the PC Period	ITT
4.1.3.4	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit Geographical Region in the PC Period	ITT
4.2 Secondary Efficacy		
4.2.1 IGA-TS		
4.2.1.1	Proportion of Participants Achieving IGA-TS by Visit in the PC Period Using Nonresponder Imputation	ITT
4.2.1.2	Proportion of Participants Achieving IGA-TS by Visit in the Extension Period	Ext-Ev
4.2.2 ITCH NRS		
4.2.2.1	Kaplan-Meier Curve of the Time to ≥ 4-Point Improvement in Itch NRS Score by Visit in the PC Period	ITT
4.2.2.2	Proportion of Participants Achieving ≥ 4-Point Improvement in Itch NRS Score by Visit in the Extension Period	Ext-Ev
4.6 Laboratory		
4.6.1.1.1	Boxplot of Mean (± SE) of Selected Laboratory Values by Visit and Treatment Group in the PC Period	Safety
4.6.1.1.2	Boxplot of Mean (± SE) of Change from Baseline in Selected Laboratory Values by Visit and Treatment Group in the PC Period	Safety
4.6.1.1.3	Boxplot of Mean (± SE) of Percent Change from Baseline in Selected Laboratory Values by Visit and Treatment Group in the PC Period	Safety
4.6.1.2.1	Boxplot of Mean (± SE) of Selected Laboratory Values by Visit and Treatment Group in the Extension Period	Ext-Ev
4.6.1.2.2	Boxplot of Mean (± SE) of Change From Baseline in Selected Laboratory Values by Visit and Treatment Group in the Extension Period	Ext-Ev
4.6.1.2.3	Boxplot of Mean (± SE) of Percent Change From Baseline in Selected Laboratory Values by Visit and Treatment Group in the Extension Period	Ext-Ev
4.6.1.3.1	Boxplot of Mean (± SE) of Selected Laboratory Values by Visit and Treatment Group for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Lipid Panel	Safety
4.6.1.3.2	Boxplot of Mean (± SE) of Change From Baseline in Selected Laboratory Values by Visit and Treatment Group Period for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Lipid Panel	Safety

Figure No.	Title	Population
4.6.1.3.3	Boxplot of Mean (± SE) of Percent Change from Baseline in Selected Laboratory Values by Visit and Treatment Group for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Lipid Panel	Safety
4.6.2.1.1	Boxplot of Mean (± SE) of Lipid Panel Values by Visit and Treatment Group in the PC Period	Safety
4.6.2.1.2	Boxplot of Mean (± SE) of Change from Baseline of Lipid Panel Values by Visit and Treatment Group in the PC Period	Safety
4.6.2.1.3	Boxplot of Mean (± SE) of Percent Change from Baseline of Lipid Panel Values by Visit and Treatment Group in the PC Period	Safety
4.6.2.2.1	Boxplot of Mean (± SE) of Lipid Panel Values by Visit and Treatment Group in the Extension Period	Ext-Ev
4.6.2.2.2	Boxplot of Mean (± SE) of Change From Baseline of Lipid Panel Values by Visit and Treatment Group in the Extension Period	Ext-Ev
4.6.2.2.3	Boxplot of Mean (± SE) of Percent Change From Baseline of Lipid Panel Values by Visit and Treatment Group in the Extension Period	Ext-Ev
4.6.2.3.1	Boxplot of Mean (± SE) of Lipid Panel Values by Visit and Treatment Group for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Lipid Panel	Safety
4.6.2.3.2	Boxplot of Mean (± SE) of Change from Baseline in Lipid Panel Values by Visit and Treatment Group for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Lipid Panel	Safety
4.6.2.3.3	Boxplot of Mean (± SE) of Percent Change from Baseline of Lipid Values by Visit and Treatment Group for Participants Who Took Only Povorcitinib 45 mg or 75 mg During Overall Period - Lipid Panel	Safety

Listings

Listing No.	Title
2.1 Demographic and Baseline Characteristics	
2.1.1.x	Participant Enrollment and Disposition Status in the PC Period
2.1.2	Participant Inclusion and Exclusion Criteria Violations
2.2 Protocol Deviations	
2.2.x	Protocol Deviations in the PC Period
2.3 Analysis Populations	
2.3	Analysis Populations
2.4 Demographic and Baseline Characteristics (including Prior and Concomitant Medications)	
2.4.1	Demographic and Baseline Characteristics
2.4.2	Disease History
2.4.3	Prior Therapy for Prurigo Nodularis
2.4.4	Medical History
2.4.5.1	Prior and Concomitant Medication in the PC Period
2.4.5.2	Concomitant Medication in the Extension Period
2.5 Drug Compliance	
2.5.1.x	Study Drug Compliance in the PC Period
2.5.2.x	Study Drug Administration in PC Period

Listing No.	Title
2.6 Efficacy	
2.6.1.x	Itch NRS Score and ≥ 4-Point Improvement Responses in the PC Period
2.6.2.x	IGA Score and IGA-TS Responses in the PC Period
2.6.3.x	Itch NRS and IGA Score in the PC Period
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
2.7 Adverse Events	
2.7.1.	Adverse Events
2.7.2.x	Serious Adverse Events in the PC Period
2.7.3.x	Grade 3 and Higher Adverse Events in the PC Period
2.7.4.x	Fatal Adverse Events in the PC Period
2.7.5.x	Treatment-Related Adverse Events in the PC Period
2.7.6.x	Adverse Events Leading to Dose Interruption in the PC Period
2.7.7.x	Adverse Events Leading to Discontinuation of Study Drug in the PC Period
2.8 Laboratory Data	
2.7.8.x	Adverse Events Requiring Concomitant Medications in the PC Period
2.8.1.1.x	Clinical Laboratory Values in the PC Period - Hematology
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2.8.1.3.x	Clinical Laboratory Values in the PC Period - Lipid Panel
2.8.1.4.x	Clinical Laboratory Values in the PC Period - Urinalysis
2.8.1.5.x	Clinical Laboratory Values in the PC Period - Thyroid Function Markers and Inflammation Marker
2.8.2.1.x	Abnormal Clinical Laboratory Values in the PC Period - Hematology
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2.8.3.x	Potentially Clinically Important Laboratory Values in the PC Period
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2.9 Vital Signs	
2.9.1.x	Vital Signs in the PC Period

Listing No.	Title
2.9.2.x	Abnormal Vital Sign Values in the PC Period
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