Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of INCB054707 in Participants With Prurigo Nodularis

NCT Number: NCT05061693

Document Date: Clinical Study Protocol Amendment 2: 06-May-2022

Clinical Study Protocol

INCB 54707-206

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of INCB054707 in Participants With Prurigo Nodularis

Product:	**INCB054707**
IND Number:	**137,156**
Phase of Study:	**Phase 2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**20 APR 2021**
Amendment 1:	**12 JUL 2021**
Amendment 2:	**06 MAY 2022**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted.
The information in this document is confidential. No part of this information may be duplicated, referenced, or transmitted in any form or by any means (electronic, mechanical, photocopy, recording, or otherwise) without prior written consent.

INVESTIGATOR'S AGREEMENT

I have read the INCB 54707-206 Protocol Amendment 2 (dated 06 MAY 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR'S AGREEMENT 2
TABLE OF CONTENTS 3
LIST OF ABBREVIATIONS 8
1. PROTOCOL SUMMARY 11
2. INTRODUCTION 19
2.1. INCB054707 19
2.2. Prurigo Nodularis 19
2.3. Study Rationale 20
2.3.1. Scientific Rationale for Study Design 21
2.3.2. Justification for Dose 21
2.3.3. Justification for Placebo 22
2.4. Benefit/Risk Assessment 22
3. OBJECTIVES AND ENDPOINTS 24
4. STUDY DESIGN 25
4.1. Overall Design 25
4.2. Overall Study Duration 25
4.3. Study Termination 26
5. STUDY POPULATION 26
5.1. Inclusion Criteria 26
5.2. Exclusion Criteria 27
5.3. Lifestyle Considerations 31
5.3.1. Meals and Dietary Restrictions 31
5.4. Screen Failures 32
5.5. Replacement of Participants 32
5.6. Data Monitoring Committee 32
6. STUDY TREATMENT 33
6.1. Study Treatment Administered 33
6.2. Preparation, Handling, and Accountability 35
6.3. Measures to Minimize Bias: Randomization and Blinding 36
6.4. Study Treatment Compliance 36

6.5. Dose Modifications....36
6.5.1. Criteria and Procedures for Dose Interruptions of Study Drug....36
6.5.2. Criteria for Permanent Discontinuation of Study Drug....39
6.6. Concomitant Medications and Procedures....39
6.6.1. Permitted Medications and Procedures....39
6.6.2. Restricted Medications and Procedures....40
6.6.3. Prohibited Medications and Procedures....40
6.6.4. Rescue Therapy....41
6.7. Treatment After the End of the Study....41
7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL....41
7.1. Discontinuation of Study Treatment....41
7.1.1. Reasons for Discontinuation....41
7.1.2. Discontinuation Procedures....42
7.2. Participant Withdrawal From the Study....43
7.3. Lost to Follow-Up....43
8. STUDY ASSESSMENTS AND PROCEDURES....43
8.1. Administrative and General Procedures....43
8.1.1. Informed Consent Process....43
8.1.2. Screening Procedures....44
8.1.3. Interactive Response Technology Procedure....45
8.1.4. Distribution of Reminder Cards and/or Diaries....45
8.1.5. Demography and Medical History....45
8.1.5.1. Demographics and General Medical History....45
8.1.5.2. Disease Characteristics and Treatment History....45
8.2. Efficacy Assessments....45
8.2.1. Health Economics....45
8.2.2. Investigator's Global Assessment....46
[redacted]....46
[redacted]....46
[redacted]....46
8.3. Patient-Reported Outcomes....46
8.3.1. eDiary....47

8.3.1.1. Itch NRS 47
[redacted] 47
[redacted] 47
[redacted] 47
[redacted] 48
[redacted] 48
[redacted] 48
[redacted] 49
[redacted] 49
8.4. Safety Assessments 49
8.4.1. Adverse Events 49
8.4.2. Physical Examinations 50
8.4.3. Vital Signs 50
8.4.4. Electrocardiograms 51
8.4.5. Laboratory Assessments 51
8.4.5.1. Pregnancy Testing 54
8.4.5.2. Serology 54
8.4.5.3. Tuberculosis Screening 54
[redacted] 55
[redacted] 55
[redacted] 56
[redacted] 56
8.7. Unscheduled Visits 56
8.8. End of Treatment and/or Early Termination 56
8.9. Follow-Up 57
9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 57
9.1. Definition of Adverse Event 57
9.2. Definition of Serious Adverse Event 58
9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events 59
9.4. Reporting of Serious Adverse Events 61
9.5. Events of Clinical Interest 62
9.6. Emergency Unblinding of Treatment Assignment 63

9.7. Pregnancy 63
9.8. Warnings and Precautions 64
9.9. Product Complaints 64
9.10. Treatment of Overdose 64
10. STATISTICS 64
10.1. Sample Size Determination 64
10.2. Populations for Analysis 64
10.3. Level of Significance 65
10.4. Statistical Analyses 65
10.4.1. Primary Analysis 65
10.4.2. Secondary Analysis 66
10.4.3. Safety Analyses 66
[redacted] [redacted] 66
[redacted] [redacted] 67
[redacted] [redacted] 67
[redacted] [redacted] 67
11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 67
11.1. Investigator Responsibilities 67
11.1.1. Identification of the Coordinating Principal Investigator 68
11.2. Data Management 68
11.3. Data Privacy and Confidentiality of Study Records 70
11.4. Financial Disclosure 71
11.5. Publication Policy 71
11.6. Study and Site Closure 72
12. REFERENCES 73
APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS 75
APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS 77
APPENDIX C. LIST OF STRONG/MODERATE SYSTEMIC CYP3A4 INHIBITORS AND STRONG SYSTEMIC CYP3A4 INDUCERS 80
APPENDIX D. INSTRUCTION TO PARTICIPANTS FOR HANDLING INCB054707 81

APPENDIX E. MANAGEMENT OF POTENTIAL HY'S LAW CASES 82
APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES 86

LIST OF TABLES

Table 1: Primary and Secondary Objectives and Endpoints....11
Table 2: Key Study Design Elements 12
Table 3: Schedule of Activities for the Placebo-Controlled Period....14
Table 4: Schedule of Activities for the Extension Period....17
[redacted] [redacted] 23
Table 6: Objectives and Endpoints 24
Table 7: Exclusionary Laboratory Values 30
Table 8: Study Drug Information....34
Table 9: Guidelines for Interruption, Restart, and Discontinuation of Study Drug Based on Platelet Count....37
Table 10: Guidelines for Interruption, Restart, and Discontinuation of Study Drug....37
Table 11: Investigator's Global Assessment 46
Table 12: Required Laboratory Analytes....53
Table 13: Populations for Analysis....65

LIST OF FIGURES

Figure 1: Study Design Schema 13
Figure 2: Role of JAK1 in Prurigo Nodularis 21

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
anti-HBc	anti–hepatitis B core
AST	aspartate transaminase
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
[redacted]	[redacted]
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
[redacted]	[redacted]

Abbreviations and Special Terms	Definition
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment Treatment Success (IGA score of 0 or 1 with ≥ 2-grade improvement from baseline)
IgE	Immunoglobulin E
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
k_a	absorption rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numerical rating scale
[redacted]	[redacted]
PD	pharmacodynamic
PDE-4	phosphodiesterase-4

Abbreviations and Special Terms	Definition
[redacted]	[redacted]
PHL	potential Hy's law
PK	pharmacokinetic
PN	prurigo nodularis
PPD	purified protein derivative
PT	prothrombin time
Q/F	apparent intercompartmental clearance
QALY	quality-adjusted life year
QD	once daily
QFT-GIT	QuantiFERON-TB Gold In-Tube test
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedules of activities
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
[redacted]	[redacted]
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th	T-helper
[redacted]	[redacted]
[redacted]	[redacted]
TYK	tyrosine kinase
ULN	upper limit of normal
VAS	visual analog scale
[redacted]	[redacted]
[redacted]	[redacted]
WBC	white blood cell
WOCBP	women of childbearing potential
[redacted]	[redacted]

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of INCB054707 in Participants With Prurigo Nodularis

Protocol Number: INCB 54707-206

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of INCB054707 in PN.	Proportion of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16.
Secondary	
To further assess the treatment effects of INCB054707.	• 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 INCB054707.	The type, frequency, and severity of AEs, including the results of physical examinations, and evaluation of vital signs, ECGs, and laboratory data.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Treatment of patients with PN
Population	Male and female participants 18 to [redacted] years of age 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.
Number of Participants	Approximately 140 participants will be randomized 1:1:1:1 to 1 of 4 treatment groups (35 participants per group).
Study Design	This is a randomized, double-blind, placebo-controlled study with a single-blind extension period. The dose of INCB054707 in the extension period will be based on efficacy response (Itch NRS and IGA) at Week 16.
Estimated Duration of Study Participation	Participants will participate for up to 48 weeks, including up to 4 weeks for screening, up to 40 weeks of treatment (16 weeks in the placebo-controlled period and 24 weeks in the extension period), and 4 weeks for safety follow-up.
DMC	Yes (internal)
Coordinating Principal Investigator	Shawn G. Kwatra, MD

Treatment Groups and Duration:

On Day 1, eligible participants will be equally randomized to 1 of 4 treatment groups (INCB054707 15 mg QD, 45 mg QD, or 75 mg QD or placebo; see Figure 1) and stratified by IGA score (3 vs 4). Participants will receive blinded study drug through Week 16.

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 are 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. Protocol-permitted rescue therapies are presented in Section 6.6.4. Participants receiving a prohibited medication (see Section 6.6.3) as rescue therapy must be withdrawn from study drug.

Based on the IGA and Itch NRS responses at Week 16, participants will receive either INCB054707 [redacted] or [redacted] QD for an additional 24 weeks in the extension period. The investigator will be aware of the dose in the extension period; the participant will remain blinded to the dose received in the extension period.

- [redacted]
- [redacted].

Figure 1 presents the study design schema. The SoA for the placebo-controlled and extension periods are presented in Table 3 and Table 4, respectively. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

Figure 1: Study Design Schema

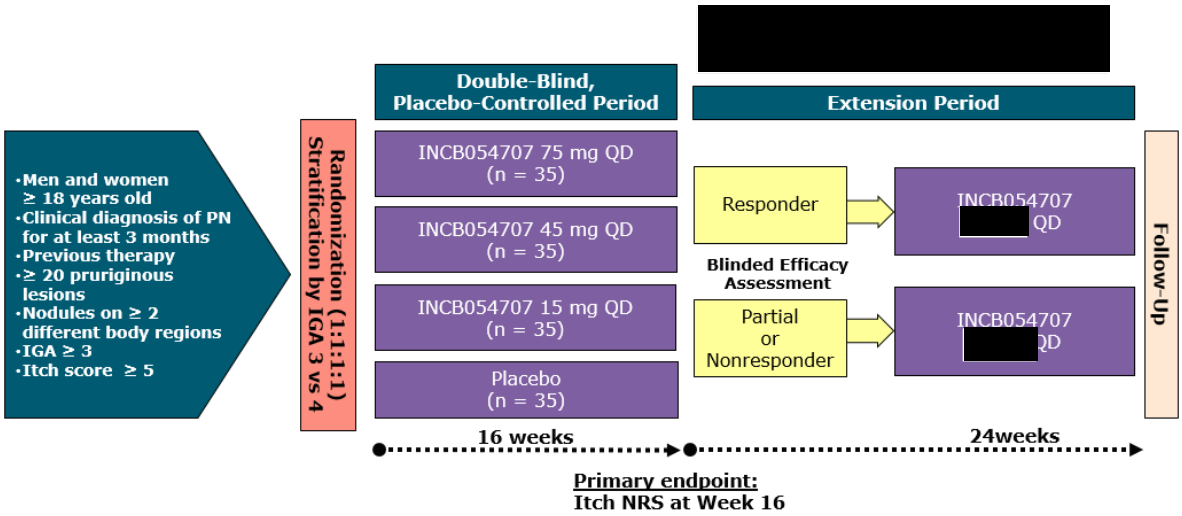


Table 3: Schedule of Activities for the Placebo-Controlled Period

Visit Day (Range)	Screening	Placebo-Controlled Treatment							Notes
	Days −28 to −1	Day 1 (Baseline)	Week 2 Remote (± 3 d)	Week 4 (± 3 d)	Week 6 Remote (± 3 d)	Week 8 (± 3 d)	Week 12 (± 3 d)	Week 16/ EOT1 (± 3 d)	Week 16 assessments must be complete before a participant can continue in the extension period.
Administrative procedures									
Informed consent	X								Section 8.1.1
Inclusion/exclusion criteria review	X	X							Section 5
Demography and medical history	X								General and disease-specific medical history. Section 8.1.5
Prior/concomitant medications	X	X	X	X	X	X	X	X	Section 6.6
Contact IRT	X	X		X		X	X	X	Section 8.1.3
Randomization		X							
Dispense study drug		X		X		X	X	X	
Study drug administered at site		X		X				X	
Collect study drug and review study drug compliance				X		X	X	X	
Distribute reminder card		X		X		X	X	X	
Assess eDiary compliance		X	X	X	X	X	X	X	
Follow-up phone call (eDiary compliance)	X								Section 8.3.1
Safety assessments									
AE assessments	X	X	X	X	X	X	X	X	If an AE is noted, relevant body systems should be physically examined. Section 8.4.1
Comprehensive physical examination	X	X						X	Section 8.4.2
Height		X							
Weight	X	X						X	
Vital signs	X	X		X		X	X	X	Section 8.4.3
12-lead ECG	X							X	Section 8.4.4

Table 3: Schedule of Activities for the Placebo-Controlled Period (Continued)

Visit Day (Range)	Screening Days −28 to −1	Placebo-Controlled Treatment Day 1 (Baseline)	Week 2 Remote (± 3 d)	Week 4 (± 3 d)	Week 6 Remote (± 3 d)	Week 8 (± 3 d)	Week 12 (± 3 d)	Week 16/ EOT1 (± 3 d)	Notes Week 16 assessments must be complete before a participant can continue in the extension period.
Efficacy assessments									
IGA	X	X		X		X	X	X	Section 8.2.2
[redacted]									
Patient-reported outcomes (Note: Should be conducted before any other assessments)									
Itch NRS	Diary is completed each evening from screening through the last dose of study drug.								Section 8.3.1.1
[redacted]									
Laboratory assessments									
TB screening	X								Table 12
Serology	X								Table 12
Chemistry assessments	X	X	X	X	X	X	X	X	Table 12
Hematology assessments	X	X	X	X	X	X	X	X	
FSH	X								Women of nonchildbearing potential. Table 12
Serum pregnancy test	X							X*	*WOCBP only. Table 12
Urine pregnancy test		X		X		X	X		WOCBP only. Positive urine test to be confirmed by serum test. Table 12
Coagulation	X					X		X	Table 12

Table 3: Schedule of Activities for the Placebo-Controlled Period (Continued)

Visit Day (Range)	Screening	Placebo-Controlled Treatment							Notes
	Days −28 to −1	Day 1 (Baseline)	Week 2 Remote (± 3 d)	Week 4 (± 3 d)	Week 6 Remote (± 3 d)	Week 8 (± 3 d)	Week 12 (± 3 d)	Week 16/ EOT1 (± 3 d)	Week 16 assessments must be complete before a participant can continue in the extension period.
Laboratory assessments (continued)									
Lipid panel		X				X		X	Table 12
Thyroid function	X							X	Table 12
Urinalysis	X					X		X	Table 12
[redacted]									

Table 4: Schedule of Activities for the Extension Period

Visit Day (Range)	Extension Treatment								Safety Follow-up	Notes
	Week 18 Remote (± 3 d)	Week 20 (± 3 d)	Week 22 Remote (± 3 d)	Week 24 (± 3 d)	Week 28 (± 3 d)	Week 32 (± 3 d)	Week 36 (± 3 d)	Week 40/ EOT2 (± 3 d)	28 Days (+ 7 d) After Last Dose	
Administrative procedures										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	Section 6.6
Contact IRT		X		X	X	X	X	X		Section 8.1.3
Distribute reminder card		X		X	X	X	X	X		
Dispense study drug		X		X	X	X	X			
Collect study drug and review study drug compliance		X		X	X	X	X	X		
Assess eDiary compliance	X	X	X	X	X	X	X	X		
Safety assessments										
AE assessments	X	X	X	X	X	X	X	X	X	If an AE is noted, relevant body systems should be physically examined. Section 8.4.1
Comprehensive physical examination								X		Section 8.4.2
Weight					X			X		
Vital signs		X		X	X	X	X	X	X	Section 8.4.3
12-lead ECG								X		Section 8.4.4
Efficacy assessments										
IGA		X		X	X	X	X	X	X	Section 8.2.2
[redacted]										
Patient-reported outcomes (Note: Should be conducted before any other assessments)										
Itch NRS	Diary is completed each evening from screening through the last dose of study drug.									Section 8.3.1.1
[redacted]										

Table 4: Schedule of Activities for the Extension Period (Continued)

Visit Day (Range)	Extension Treatment								Safety Follow-up	Notes
	Week 18 Remote (± 3 d)	Week 20 (± 3 d)	Week 22 Remote (± 3 d)	Week 24 (± 3 d)	Week 28 (± 3 d)	Week 32 (± 3 d)	Week 36 (± 3 d)	Week 40/ EOT2 (± 3 d)	28 Days (+ 7 d) After Last Dose	
[redacted]										
Laboratory assessments										
Chemistry assessments	X	X	X	X	X	X	X	X	X	Table 12
Hematology assessments	X	X	X	X	X	X	X	X	X	
Serum pregnancy test									X	WOCBP only. Table 12
Urine pregnancy test		X		X	X	X	X	X		WOCBP only. Positive urine test to be confirmed by serum test. Table 12
Coagulation				X				X		Table 12
Lipid panel				X				X		Table 12
Thyroid function								X		Table 12
Urinalysis				X				X		Table 12
[redacted]										

2. INTRODUCTION

2.1. INCB054707

INCB054707 is an oral JAK inhibitor with selectivity for JAK1 that is currently under development for the treatment of patients with HS and vitiligo. Proinflammatory cytokines are strongly implicated in the pathogenesis of several dermatologic diseases, such as HS, atopic dermatitis, plaque psoriasis, vitiligo, and PN. Additionally, JAKs mediate extracellular signals from a number of relevant proinflammatory cytokines and growth factors upregulated in those disease states. Further, a Phase 2 study of INCB054707 in participants with HS (NCT03607487) demonstrated proof of concept by showing a decrease in abscess and inflammatory nodules, as well as improvements in skin pain and quality of life. This supports the investigation of INCB054707 in a Phase 2 dose-ranging study in participants with PN.

2.2. Prurigo Nodularis

Prurigo nodularis is a chronic skin disorder affecting primarily older adults and is characterized by firm, dome-shaped, intensely pruritic nodules ranging in size from a few millimeters to several centimeters. The nodules are often symmetrically distributed on the extensor surfaces of the arms and legs and on the trunk. The itch generally precedes the nodules and is thought to be neurogenic; however, the underlying cause of the itch is not known. In a subset of patients with chronic pruritus, PN occurs as a result of continuous scratching. Typically, the upper back is spared, as this is an area that patients cannot reach to scratch [redacted]

Prurigo nodularis has an estimated prevalence of 72 per 100,000 persons in the US, based on people with health insurance (Huang et al 2020). Reports vary on whether it occurs more frequently in women versus men (Huang et al 2020) or occurs equally in men and women (Elmariah et al 2021, Pereira et al 2018). People with black skin are substantially more likely to have PN than people with white skin (McColl et al 2021). In particular, 1 study found that African American patients were 3.4 times more likely to have PN than White patients (Boozalis et al 2018).

Quality of life can be substantially and negatively impacted by PN (Kwatra 2020), in particular, sleep disturbance, impact on job performance, and avoidance of social activities (Todberg et al 2020). In addition, the burden of systemic comorbidities in PN often exceeds that of other inflammatory skin disorders (ie, atopic dermatitis or psoriasis). Prurigo nodularis is associated with increased rates of mental health (specifically anxiety and depression) and endocrine, cardiovascular, and renal disorders as well as HIV infection and malignancy (Dazzi et al 2011, Huang et al 2020, Kowalski et al 2019). Approximately half of all patients with PN report a history of atopic dermatitis (Iking et al 2013).

Pharmacologic therapy with first-generation sedating antihistamines (eg, hydroxyzine, diphenhydramine) administered at bedtime may be useful in controlling nocturnal pruritus. Both selective serotonin reuptake inhibitors and tricyclic antidepressants are also used for the treatment of chronic pruritus, especially when a component of depression is present [redacted]

Superpotent topical corticosteroids are considered first-line therapy (Williams et al 2020). Patients with widespread disease may be treated with phototherapy (Kowalski et al 2019). Patients with recalcitrant PN may be given systemic treatments including systemic immunosuppressants, thalidomide, lenalidomide, and anticonvulsants (Tsianakas et al 2016). These treatments are associated with potential significant toxicity, and their efficacy in patients with recalcitrant PN has not been established [redacted].

2.3. Study Rationale

Inflammatory cells, including T cells, eosinophils, and mast cells, are increased in patients with PN and secrete neurotrophins that promote neurogenic inflammation (Kwatra 2020, Perez et al 1993). Central to the pathogenesis of PN is a robust inflammatory response and intense itch caused by mediators such as IL-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides (Almeida et al 2004, Zeidler et al 2018).

The role of Th1 and Th2 cytokines in the pathogenesis of PN has been evaluated by examining the cytokine signatures in the epidermis in 22 cases of PN, using STAT 1, 3, and 6 (Fukushi et al 2011). In 19 of the 22 cases of PN, the entire epidermis stained with anti-pSTAT 6, a marker for the Th2 cytokines IL-4, IL-5, and IL-13. Only 8 cases showed scattered staining with anti-pSTAT 1, a marker for the Th1 cytokines interferon gamma and IL-27. [redacted]

The improvements in itch seen with JAK inhibitors are well known, and INCB054707 should provide relief for itch, which is one of the most bothersome symptoms of PN (Wang and Kim 2020).

[redacted]

[redacted]

2.3.1. Scientific Rationale for Study Design

This study will examine the efficacy and safety of 3 doses of INCB054707 (15, 45, and 75 mg QD) versus placebo as proof of concept and dose ranging. The placebo-controlled period will be 16 weeks, and the dose in the extension period will be determined by IGA and Itch NRS responses at Week 16. [redacted] This design will provide a well-controlled assessment of the efficacy of INCB054707 in PN while minimizing the treatment duration for participants assigned to placebo. In addition, it will help determine the possibility of maintaining a response at a lower exposure as well as the possibility of a more robust response at a higher exposure if the initial dose was not sufficient to elicit a therapeutic response. Further, the 24-week extension period will provide an adequate duration to assess the maintenance of the response for responders or the potential improvement of response for nonresponders.

[redacted]

[redacted]

2.3.3. Justification for Placebo

The comparison to placebo is relevant to better understand the effect of an oral systemic JAK1 inhibitor in the treatment of PN. The use of placebo is justified considering that there are no available PN-specific therapies to be used as a comparator and that delaying treatment does not pose excessive harm to patients (Millum and Grady 2013). In addition, participants who have a substantial worsening of PN during the placebo-controlled period may receive rescue therapy (see Section 6.6.4 for allowed recue therapies). After the 16-week placebo-controlled period, all participants will receive INCB054707 [redacted] or [redacted] QD for up to 24 weeks in the extension period.

2.4. Benefit/Risk Assessment

INCB054707 has been studied in 2 healthy participant studies (76 participants) and 2 studies in participants with HS (45 participants, NCT03569371 and NCT03607487).

In healthy participants, single doses of INCB054707 up to 405 mg and multiple doses of INCB054707 up to 120 mg QD were administered for up to 10 days. The most common TEAE was mild to moderate headache in 31% of participants who received INCB054707 in the multiple-dose study; the events were not dose-dependent and resolved spontaneously following discontinuation of INCB054707.

The studies in participants with HS examined QD doses of 15, 30, 60, and 90 mg and placebo for up to 8 weeks. Transient and asymptomatic thrombocytopenia was observed after 4 weeks of exposure in 4 of 8 participants who received INCB054707 90 mg QD. The dose was interrupted for a maximum of 2 weeks, and the thrombocytopenia resolved without intervention; participants resumed treatment with INCB054707 90 mg QD and completed the study without clinical sequelae or re-emergence of thrombocytopenia. In addition, Hgb levels remained within normal limits and were mostly unchanged during the study, and neutrophil counts showed a mild dose-dependent decrease within normal limits. Across the 2 studies, the most common TEAE was fatigue, observed in 6 of the 36 participants (17%). Mild-to-moderate headache was observed in 11% of the participants exposed to INCB054707 compared with 22% of the participants exposed to placebo. No serious or fatal TEAEs were reported in the studies; more details are provided in the IB.

Based on the available nonclinical and clinical data, the potential risks to participants are summarized in [redacted] More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCB054707 may be found in the IB.

INCB054707 is the first JAK inhibitor being studied in a randomized clinical study in participants with PN, so the benefit is unknown. Based on the mechanism of action of INCB054707, it is expected that participants will see a reduction in itch as well as improvement in PN lesions (see Section 2.3.1).

[redacted]

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of INCB054707 in PN.	Proportion of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16.
Secondary	
To further assess the treatment effects of INCB054707.	• 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 INCB054707.	The type, frequency, and severity of AEs, including the results of physical examinations, and evaluation of vital signs, ECGs, and laboratory data.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This study has a 16-week, randomized, double-blind, dose-ranging, placebo-controlled period and a 24-week, single-blind extension period. The study will include approximately 140 men and women 18 to [redacted] years of age 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.

After signing the ICF, screening assessments may be completed over a period of up to 28 days. On Day 1, eligible participants will be equally randomized to 1 of 4 treatment groups (INCB054707 15 mg QD, 45 mg QD, or 75 mg QD or placebo; see Figure 1) and stratified by IGA score (3 vs 4). Participants will receive blinded study drug through Week 16.

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 are 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. Protocol-permitted rescue therapies are presented in Section 6.6.4. Participants receiving a prohibited medication (see Section 6.6.3) as rescue therapy must be withdrawn from study drug.

Based on the IGA and Itch NRS responses at Week 16, participants will receive either INCB054707 [redacted] or [redacted] QD for an additional 24 weeks in the extension period. The investigator will be aware of the dose in the extension period; the participant will remain blinded to the dose received in the extension period.

- [redacted]
- [redacted]

After the last dose of study drug, participants will be followed for safety, with a safety visit performed at least 28 days after the last dose of study drug.

Figure 1 presents the study design schema. The SoA for the placebo-controlled and extension periods are presented in Table 3 and Table 4, respectively. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The COVID-19 global pandemic may present challenges to the normal conduct of this study (including AE and laboratory assessments), requiring the outline of potential mitigation strategies described in Appendix B. Participants do not need to stop treatment in the study to receive a COVID-19 vaccine.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure for the last participant in the study globally.

It is estimated that an individual will participate for approximately 11 months, including up to 28 days for screening, up to 40 weeks of treatment (including the placebo-controlled and extension periods, as long as participants are receiving benefit and have not met any criteria for study withdrawal), and 28 (+ 7) days for follow-up after the last dose of study drug.

A participant is considered to have completed the study if he/she has completed both the placebo-controlled and the extension periods of the study. The study is considered completed when the last participant's last visit has occurred.

4.3. Study Termination

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Men and women 18 to [redacted] years of age.
3. Clinical diagnosis of PN for at least 3 months before screening.

   Note: Diagnosis may be based on investigator assessment and study participant interview.
4. Inadequate response or intolerant to ongoing or prior PN therapy.

   Note: Previous PN therapy may include any treatment (including over-the-counter products) intended to treat PN symptoms.
5. ≥ 20 pruriginous lesions at screening and Day 1.

   Note: Pruriginous lesions may include nodules, papules, plaques, umbilicated ulcers, or ulcers.

6. Pruriginous lesions on ≥ 2 different body regions at screening and Day 1.

   Note: Pruriginous lesions may include nodules, papules, plaques, umbilicated ulcers, or ulcers.

7. IGA score ≥ 3 at screening and Day 1.
8. Pruritus as defined by the following:
   a. Screening: Itch NRS score ≥ 5 based on recall for the week preceding screening.
   b. Day 1: Average Itch NRS ≥ 5 for the week before Day 1. Note: Participants must have at least 4 nonmissing Itch NRS daily scores out of the 7 days before Day 1 to calculate an average and be randomized.
9. Willingness to avoid pregnancy or fathering children based on the criteria below.
   a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Female participants who are not of childbearing potential or, if of childbearing potential, must have a negative pregnancy test at screening (serum) and before the first dose on Day 1 (urine). Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study drug and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

5.2. Exclusion Criteria

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

1. Have chronic pruritus due to a condition other than PN (eg, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease, excoriation syndrome, cholestatic liver disease, chronic kidney disease).
2. Have neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis.
3. Current use of a medication known to cause pruritus.
4. Have concurrent conditions and history of other diseases as follows:
   a. Thrombocytopenia, coagulopathy, platelet dysfunction, or history of thrombotic events.
   b. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton' syndrome), pigmentation, or extensive scarring that in the opinion of the

investigator may interfere with the evaluation of PN lesions or assessments of efficacy or compromise participant safety.

c. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the Day 1 visit.
d. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox, clinically infected atopic dermatitis, impetigo) within 1 week before the Day 1 visit.
e. Current herpes zoster infection, a history of disseminated herpes simplex, or a history of herpes zoster.
f. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
g. History of malignancy, including melanoma, lymphoma, and leukemia within 5 years before Day 1, other than a successfully treated nonmetastatic cutaneous squamous cell carcinoma, basal cell carcinoma, or localized carcinoma in situ of the cervix.
h. Albinism.

[redacted]

[redacted]

[redacted]

17. Evidence of HBV or HCV infection or risk of reactivation. Participants cannot be positive for HBsAg, anti–hepatitis B core antibody, or HCV antibody; participants also cannot be positive for HBV DNA or HCV RNA in case these reflexive assessments are required to be performed.

    Note 1: Participants with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody (hepatitis B surface antibody) against HBsAg as the only evidence of prior exposure may participate in the study.

    Note 2: Participants with a history of HCV infection who are antibody positive and have successfully completed treated > 12 weeks before screening, and have no detectable HCV RNA, are allowed in the study.

18. Known HIV infection.

19. Evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (ie, TB), as defined by the following:
    a. A positive QFT-GIT or positive Mantoux/PPD tuberculin skin test performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility unless other criteria as described here are applicable. It is recommended that participants with a history of Bacille Calmette-Guérin vaccination be tested with the QFT-GIT, because the Mantoux/PPD tuberculin skin test may be positive due to vaccination. A QFT-GIT or Mantoux/PPD tuberculin skin test is not required if the participant has previously received a documented adequate course of therapy for either latent or active TB infection.
    b. A history of either untreated or inadequately treated latent or active TB infection.
    c. If a participant has previously received an adequate course of therapy for either latent TB infection (9 months of isoniazid in a locale where rates of primary multidrug TB resistance are < 5% or an acceptable alternative regimen) or active TB infection (an acceptable multidrug regimen), neither a QFT-GIT nor a Mantoux/PPD tuberculin skin test is needed, but a chest x-ray(s) or other appropriate diagnostic image, performed within 3 months of Day 1, is required. To be considered eligible for the study, the x-ray(s) must be negative for active TB infection as determined by a qualified radiologist. Documentation of adequate treatment for TB and negative chest x-ray(s) results must be obtained prior to Day 1.
    d. A participant who is currently being treated for active or latent TB infection is to be excluded.
20. Pregnant or lactating participants or those considering pregnancy.
21. History of alcoholism or drug addiction within 1 year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the administration schedule and study assessments.
22. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
23. Planned or expected major surgery within the timelines of study duration.
24. Concurrent enrollment in another clinical study.

5.3. Lifestyle Considerations

Participants are not allowed to use tanning beds during the study.

5.3.1. Meals and Dietary Restrictions

Participants must abstain from consumption of grapefruit or grapefruit juice (pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) and of Seville oranges from 14 days before the start of study drug until after the final dose of study drug.

Participants must abstain from consumption of dietary supplements containing St John's wort (Hypericum perforatum) from 14 days before the start of study drug until after the final dose of study drug.

5.4. Screen Failures

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

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

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

5.6. Data Monitoring Committee

This study will use an internal DMC to monitor safety. There will be 1 planned DMC review after randomization of the initial approximately 40 participants in the study and their respective completion of the Week 16 visit. The DMC will meet for at least 1 additional review at a time to be determined after the first review meeting. The DMC members will be blinded to participants' treatment assignment for the initial safety review; however, the DMC members may request unblinding at any time.

The members of the DMC will not be involved with the study in any other way. The DMC charter will describe the composition, responsibilities, governance (including the roles and responsibilities of the various members, the sponsor, and protocol team), and requirements for and proper documentation of DMC meetings (reports, minutes, and recommendations).

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 8 presents the study drug information.

Participants will record study drug administration in a daily diary. Further information regarding study drug administration is provided in Appendix D.

The COVID-19 global pandemic may present challenges to the normal conduct of this study, requiring the outline of potential mitigation strategies described in Appendix B. Participants do not need to interrupt study drug to receive the COVID-19 vaccine.

Table 8: Study Drug Information

	Placebo-Controlled Period, Double-Blind (16 Weeks)		Extension Period, Single-Blind (24 Weeks)
	Study Treatment 1	**Study Treatment 2**	**Study Treatment – Extension**
Study treatment name:	INCB054707	Matching placebo	INCB054707
Mechanism of action:	JAK inhibitor	Not applicable	JAK inhibitor
Dosage formulation:	Tablet, oral	Tablet, oral	Tablet, oral
Unit dose strength(s) /dosage level(s):	• 15 mg = [redacted] INCB054707 [redacted] and [redacted] placebo tablets • 45 mg = [redacted] INCB054707 [redacted] and [redacted] placebo tablets • 75 mg = [redacted] INCB054707 [redacted]	• Placebo = [redacted] placebo tablets	• [redacted] = [redacted] INCB054707 [redacted] tablets and [redacted] placebo tablets • [redacted] = [redacted] INCB054707 [redacted] tablets
Administration instructions:	INCB054707 or matching placebo will be taken orally QD, preferably in the morning, with a full glass of water, without regard to food. Note: Dose will be administered at the study site at the Week 4 and Week 16 visits. Participants will withhold self-administration on the days of those visits.		INCB054707 will be taken orally QD, preferably in the morning, with a full glass of water, without regard to food.
Packaging and labeling:	INCB054707 will be provided as [redacted] tablets; placebo tablets will match the INCB054707 tablets in smell, taste, and appearance. Tablets will be packaged in blister cards. Each container will be labeled as required per country requirement.		
Storage:	[redacted]		
Status of treatment in participating countries:	Investigational		

6.2. Preparation, Handling, and Accountability

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

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including tablet counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol (see Appendix D). The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

The COVID-19 global pandemic may present challenges to the normal conduct of this study, requiring the outline of potential mitigation strategies described in Appendix B.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system (see Section 8.1.3). Participant randomization will be stratified based on IGA score on Day 1 (3 vs 4). Once a randomization number has been assigned, it must not be reassigned. Full details will be provided in the IRT Study Reference Manual.

Study drug will be dispensed at study visits summarized in the SoA (see Table 3 and Table 4).

Returned study drug should not be redispensed to participants.

Participants, investigators, and the sponsor will remain blinded to each participant's treatment assignment during the placebo-controlled period. The participant will remain blinded to the dose of INCB054707 during the extension period. Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.6 and refer to the IRT Manual).

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Compliance with study drug will be monitored by the study site based on the drug accountability and reported in the eCRF. Participants will be instructed to bring all unused study drug with them to study visits in order for site personnel to conduct tablet counts to assess study drug accountability.

Participants' compliance must be within [redacted], assessed at each study visit. If outside of this range, it will be considered a protocol deviation. Participants consistently noncompliant with the study drug may be withdrawn from the study. The decision on withdrawal will be made by the investigator after consultation with the sponsor, and relevant correspondence will be archived in the site study file.

6.5. Dose Modifications

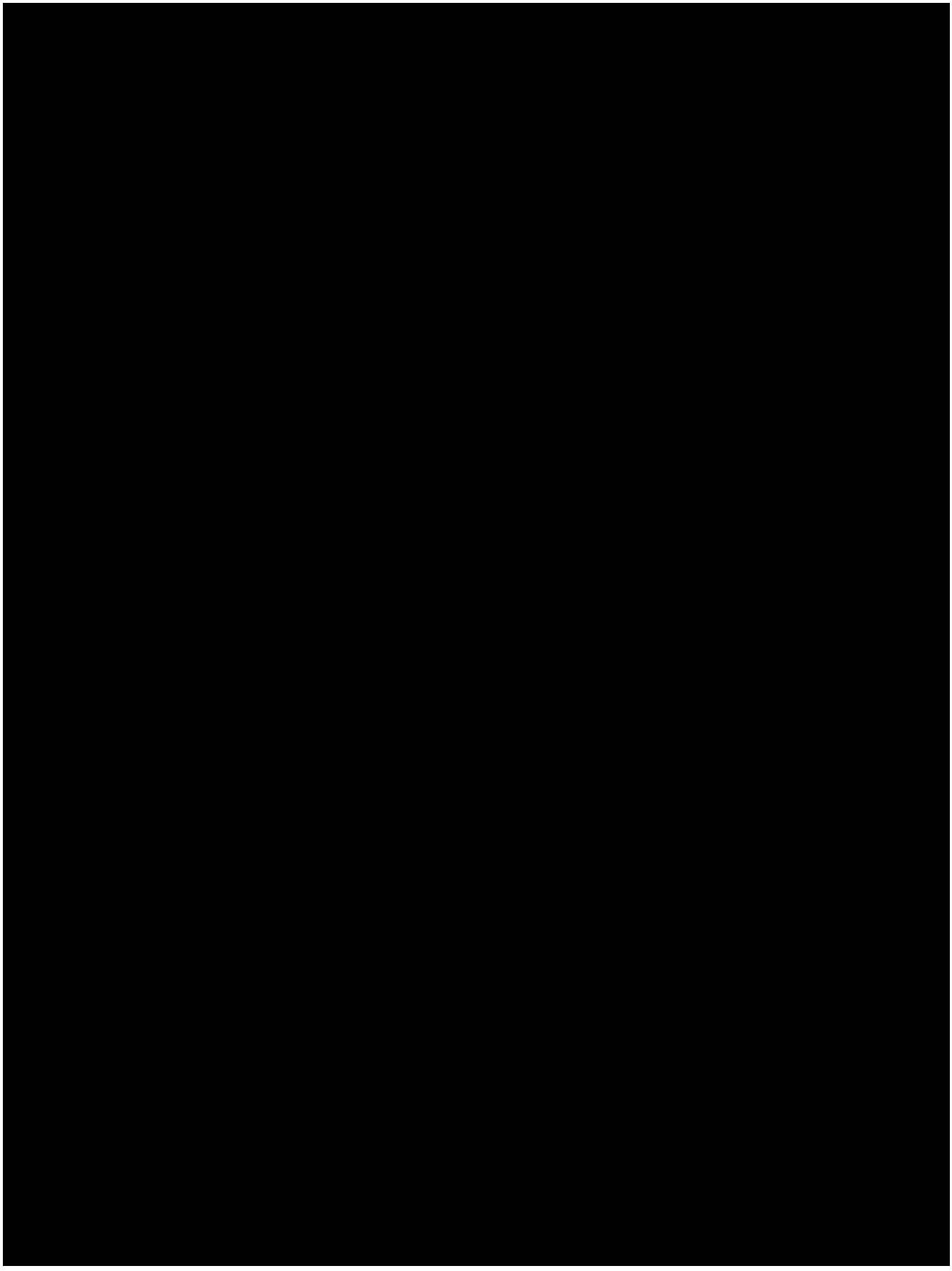
No dose modifications will be allowed during the placebo-controlled or extension periods.

[redacted]

In some circumstances, it may be necessary to temporarily interrupt treatment with study drug as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug.

[redacted]

[redacted]



6.5.2. Criteria for Permanent Discontinuation of Study Drug

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

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.

Table 9 and Table 10 provide specifics on further reasons for permanent discontinuation of study drug.

If a participant has worsening of PN and is given a prohibited medication (see Section 6.6.3) for disease control, they must be permanently discontinued from the study. Permitted medications to control PN are noted in Section 6.6.4.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any medication or procedure received up to 12 weeks before baseline through 30 days after the last dose of study drug will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded.

Other relevant medications or procedures received more than 12 weeks before the first dose of study drug may be recorded in the eCRF at the discretion of the investigator or at the request of the sponsor based on emerging events during the study.

Concomitant medications administered more than 30 days after the last dose of study drug for treatment of SAEs should be reported until the SAE is no longer being followed (see Section 8.9).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

- Use of bland emollients and sunscreen agents is permitted.
- Concomitant oral vitamins, herbal supplements, and other skin products should be approved by the investigator and ideally should remain stable during the study.
- Use of corticosteroid inhalers and intranasal sprays is permitted.
- Use of oral nonsedating antihistamines for conditions other than PN is permitted.
- Low-dose acetylsalicylic acid (≤ 100 mg QD) is permitted for the purpose of cardiovascular prophylaxis at the discretion of the investigator.
- A stable dose of gabapentin or pregabalin for a condition other than PN or for PN if on a stable dose for ≥ 6 months before screening is permitted.

Medications and procedures not mentioned as restricted or prohibited will be by default allowed.

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Use of oral corticosteroids for ≤ 7 days, if deemed acceptable by the investigator and the sponsor, is allowed for nondermatologic conditions (eg, asthma exacerbation, bronchitis).
- Permitted rescue therapies as described in Section 6.6.4.

[redacted]

6.6.4. Rescue Therapy

The initiation of non–study drug therapy to treat worsening of pruritus or PN lesions, or flare of previously inactive skin disease, is strongly discouraged throughout the placebo-controlled period. If deemed to be medically necessary by the investigator, rescue treatments for PN noted below may be added to the study drug after Week 4:

- Sedating antihistamine
- Low- or medium-potency topical corticosteroid (Grades 4-7, Ference and Last 2009)
- Topical calcineurin inhibitor
- Topical PDE-4 inhibitor

If rescue medication is to be added, the efficacy and safety assessments for the visit should be completed before the start of rescue therapy.

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 are allowable at any time during the study in participants who have substantial worsening of PN from baseline (as determined by the investigator). The date and time of rescue medication administration as well as the name and dose regimen of the rescue medication must be recorded in the eCRF.

The participant may remain on study drug, unless the rescue therapy is a prohibited medication or procedure (see Section 6.6.3).

6.7. Treatment After the End of the Study

Upon completion of the 40 weeks of treatment, participants will not be provided additional treatment within this study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does not want to be followed any longer; in this case no further data, except data in the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.

- Unacceptable toxicity as noted in Section 6.5.
- Had worsening disease and received a prohibited medication as noted in Section 6.6.3.
- The participant received rescue therapy that is noted as a prohibited medication or procedure (see Section 6.6.3).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

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

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. When a participant is withdrawn from the study, the EOT visit procedures should be performed; if possible, the safety follow-up visit should also be conducted within 28 (+ 7) days of the last dose of study drug.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 and Table 4 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.

  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

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

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

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IRT will be contacted to randomize the participant and obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to dispense medication to the participant and to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and/or Diaries

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit [redacted]

Participants will be instructed on the use of the drug administration diary. [redacted] Daily study drug administration will be recorded in the diary and verified by the study investigator/designee at study visits as shown in Table 3 and Table 4.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, Fitzpatrick scale score, nicotine use, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment that is considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's PN, including date of diagnosis, relevant disease characteristics, and prior treatments, including systemic treatments, phototherapy, and surgical procedures, will be collected at screening. A medical or surgical history of other conditions related to PN or relevant to the conduct of this clinical trial will also be collected at screening.

8.2. Efficacy Assessments

8.2.1. Health Economics

Not applicable.

8.2.2. Investigator's Global Assessment

The IGA for chronic prurigo considers the number of pruriginous lesions, which includes papules, nodules, plaques, umbilicated ulcers and ulcers, and uses them as an overall severity rating on a scale of 0 to 4 (Zeidler et al 2021) as noted in Table 11, and will be performed at the visits noted in the SoA (see Table 3 and Table 4).

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

Table 11: Investigator's Global Assessment

Grade	Severity	Description
0	Clear	No pruriginous 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)

[redacted]

8.3. Patient-Reported Outcomes

For all patient-reported outcome 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.

8.3.1. eDiary

Participants will be issued a handheld device (eDiary). Each participant will be instructed to complete the diary each evening beginning on the day of screening through Week 40 or treatment discontinuation. Compliance with the eDiary will be assessed electronically at the visits noted in the SoA (see Table 3 and Table 4). If the participant is not completing the eDiary frequently enough, the site staff will be informed so compliance can be addressed in a timely manner.

Study sites will contact participants 1 week before the baseline visit to confirm compliance with eDiary assessments to ensure information is available to allow randomization if appropriate.

8.3.1.1. Itch NRS

Each evening, the participant will assess their worst level of itch during the past 24 hours on a scale of 0 to 10.

[redacted]

[redacted]

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Table 3 and Table 4). See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

The COVID-19 global pandemic may present challenges to the normal conduct of this study, requiring the outline of potential mitigation strategies described in Appendix B.

8.4.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug. Adverse events for randomized participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any

qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study drug/procedures, or caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

If an AE is noted, a targeted physical examination should be conducted as indicated by the symptoms reported by the participant or other findings (eg, laboratory abnormalities). Abnormalities that are considered clinically significant in the judgment of the investigator (or designee) are to be reported as AEs.

All SAEs will be reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

Adverse events will also be assessed remotely, via a phone/video call conducted by the study site, for visits at Weeks 2, 6, 18, and 22 (see Table 3 and Table 4).

8.4.2. Physical Examinations

A comprehensive physical examination should be conducted at the visits noted in the SoA (see Table 3 and Table 4). The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

Height will be assessed on Day 1. Body weight will be assessed on Day 1 and at Weeks 16, 28, and 40 or at the EOT visit if the participant discontinues study drug.

As noted in Section 8.4.1, a targeted physical examination should be conducted as indicated by the symptoms reported by the participant or other findings (eg, laboratory abnormalities). Abnormalities that are considered clinically significant in the judgment of the investigator (or designee) are to be reported as AEs.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits.

8.4.3. Vital Signs

Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature and will be collected at the visits noted in the SoA (see Table 3 and Table 4). If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

8.4.4. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Table 3 and Table 4) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals; if necessary, calculation of such parameters is also acceptable if the ECG machine does not perform it automatically. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. Prolonged QTcF values of ≥ 450 milliseconds are to be confirmed by performing 2 additional ECGs (within the next 5 minutes) and averaging the results to determine the averaged value.

Additional 12-lead ECGs may be performed at other visits as deemed clinically necessary. Electrocardiograms will be interpreted by the investigator at the site or designee, and the results will be used for immediate management of the participant's care. The decision to include or exclude a participant or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. ECGs should be performed in line with local standards and results reported in the eCRF.

8.4.5. Laboratory Assessments

See Table 12 for the list of clinical laboratory tests to be performed, and Table 3 and Table 4 for the laboratory assessment visit schedule. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). [redacted] Additional testing may be required by the investigator or sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and Table 3 and Table 4.

To reduce the burden of frequent on-site visits, Weeks 2, 6, 18, and 22 are planned as remote visits (see Table 3 and Table 4). The study site will contact the participant via video/phone call and blood samples will be collected via home nursing. Should the participant prefer to attend the visit on-site, this will not be considered a protocol deviation.

In case of COVID-19–related conditions, the sites may adopt remote participant management in addition to the visits listed above. Further details are provided in Appendix B.

Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the

participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 (+ 7) days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If screening laboratory assessments are performed more than 32 days before Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Day 1.

Laboratory sample collection on Day 1 must be performed before study drug administration.

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

Table 12: Required Laboratory Analytes

<table>
<tr><th>Blood Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Serology / Infection</th><th>Pregnancy Testing</th></tr>
<tr>
<td rowspan="3">• Albumin
• ALP
• ALT
• AST
• Bicarbonate or CO_2
• Blood urea nitrogen or urea
• Calcium
• Chloride
• Creatine kinase
• Creatinine
• eGFR
• Glucose
• GGT
• Lactate dehydrogenase
• Phosphate
• Potassium
• Sodium
• Total bilirubin
• Direct bilirubin (if total bilirubin is elevated above 1.5 × ULN)
• Total protein</td>
<td rowspan="3">Complete blood count, including:
• Hgb
• Mean corpuscular volume
• Hematocrit
• Platelet count
• Mean platelet volume
• In samples with abnormalities in platelet count or size distribution (as indicated by an automated analyzer), a blood film should be examined.
• Red blood cell count
• Red blood cell distribution width (RDW)
• WBC count
Differential count (% and absolute values), including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td>
<td>• Color and appearance
• pH and specific gravity
• Bilirubin
• Glucose
• Ketones
• Leukocyte esterase
• Nitrite
• Occult blood
• Protein
• Microscopic evaluation (in case of abnormal urinalysis results)</td>
<td>• HBsAg*
• HBsAb
• HBcAb*
• HCVAb*
• HIV
• QuantiFERON-TB Gold test

*Note: If either HBsAg or HBcAb is positive, a reflexive HBV DNA must be obtained. If HCVAb is positive, a reflexive HCV RNA must be obtained.</td>
<td>Women of nonchildbearing potential will have FSH tested at screening.
Women of childbearing potential will require the following:
• Serum pregnancy test at screening, the Week 16 visit, and the safety follow-up visit.
• Urine pregnancy test at all other in-clinic visits and as medically indicated or per country or institutional requirements.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td>
</tr>
<tr><th>Lipid Panel</th><th>Coagulation</th><th>Thyroid Function Markers</th></tr>
<tr>
<td>• Total cholesterol
• Triglycerides
• LDL
• HDL

Note: Fasting is not required.</td>
<td>• PT
• INR</td>
<td>• TSH
• Free T4

Inflammation Markers
• hsCRP
• IgE</td>
</tr>
</table>

GGT = gamma-glutamyl transferase; HBsAb = hepatitis B surface antibody; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; T4 = thyroxine; TSH = thyroid-stimulating hormone.
Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
Note: Alternative tests (ie, CO_2 or CO_2 Combining Power or HCO_3) are also allowed as per regional standard of care.

8.4.5.1. Pregnancy Testing

At screening, women of nonchildbearing potential will have an FSH assessment. Women of nonchildbearing potential are defined as surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, defined as amenorrhea ≥ 12 months prior to screening.

Women of childbearing potential will have serum and urine pregnancy testing performed throughout the study as outlined in the SoA (see Table 3 and Table 4), as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement.

If a urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.4.5.2. Serology

Hepatitis B and C and HIV screening assessments will be performed at the screening visit to rule out infection; required analytes are shown in Table 12. Generally, hepatitis and HIV tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

Eligibility criteria for participants with a history of HCV infection should generally require participants to have completed curative antiviral treatment and require HCV viral quantitative RNA below the limit of quantification 12 weeks after the end of HCV therapy. A patient who is HCVAb positive but HCV RNA negative due to prior treatment or natural resolution should be eligible. Discussion with the sponsor is required.

Reactivation of HBV can occur in chronic carriers of HBV infection (HBsAg-positive, undetectable or low HBV DNA, and normal ALT) who are not on HBV therapy or in individuals who have serologic evidence of a resolved prior HBV infection (ie, HBsAg-negative and anti-HBc–positive). While HBsAg-negative, anti-HBc–positive patients are at lower risk of HBV reactivation compared with HBsAg-positive patients, risk of HBV reactivation should be considered in all participants. Discussion with the sponsor is required.

Participants with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against HBsAg as the only evidence of prior exposure may participate in the study.

8.4.5.3. Tuberculosis Screening

At the time of screening, all participants will undergo TB screening. Depending on the TB status of the participant, different assessments may be performed.

The QFT-GIT is the preferred testing method. If the QFT-GIT cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative (eg, indeterminate), then participants may be screened using the PPD tuberculin skin test (Mantoux

method; see Note 1) with approval of the medical monitor (or designee). The QFT-GIT is an indirect test for *Mycobacterium tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography (see Note 2), and other medical and diagnostic evaluations.

It is recommended that participants with a history of Bacille Calmette-Guérin vaccination be tested with the QFT-GIT, because the Mantoux/PPD tuberculin skin test may be positive due to vaccination.

A QFT-GIT or Mantoux/PPD tuberculin skin test is not required if the participant has previously received a documented adequate course of therapy for either latent TB infection (eg, 9 months of isoniazid in a locale where rates of primary multidrug TB resistance are < 5% or an acceptable alternative regimen) or active TB infection (an acceptable multidrug regimen). In such cases, a chest x-ray(s) or other appropriate diagnostic image, performed within 3 months of Day 1, is required (see Note 2). To be considered eligible for the study, the x-ray(s) must be negative for active TB infection as determined by a qualified radiologist (see Note 2). Documentation of adequate treatment for TB and negative chest x-ray(s) results must be obtained prior to Day 1.

Note 1: If the QFT-GIT cannot be performed, or if the results cannot be determined to be positive or negative (eg, indeterminate), then participants may be screened using the PPD tuberculin test (Mantoux method), with the approval of the medical monitor (or designee).

Participants must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the past 3 months. The test should be performed according to local standards with induration of < 5 mm required for inclusion.

Note 2: At the discretion of the investigator or medical monitor (or designee), participants may be required to have a chest x-ray (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, computed tomography or magnetic resonance imaging) taken at screening, or previously taken within 3 months prior to Study Day 1, and read by a qualified radiologist to potentially distinguish between latent and active TB. Documentation of adequate treatment for TB and negative chest x-ray(s) results must be obtained prior to Day 1.

8.7. Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's (or designee's) discretion and appropriate clinical and laboratory tests may be performed as clinically indicated.

If there is a potential clinically significant abnormality in hematology or chemistry assessments (particularly in platelet count) during the study, an unscheduled visit within the following week should occur to repeat laboratory assessments (further details are provided in Table 9 and Table 10). The investigator must inform and consult the sponsor (or designee) regarding any hematologic abnormality.

8.8. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug, whether the participant is terminating the study early or the participant has completed the study, the appropriate EOT visit should be conducted (EOT1 or EOT2). If the EOT visit coincides with a regular study visit, the EOT evaluations corresponding with the study period will supersede those of that scheduled visit, and the data should be entered in the appropriate EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit (EOS).

8.9. Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit (EOS), which should occur approximately 30 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study drug or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. In exceptional cases when the participant cannot return to the site for the safety follow-up visit, the participant should be contacted by telephone/video call for assessment of AEs and SAEs and the site should properly document the contact.

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

9.1. Definition of Adverse Event

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

- A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. The procedure should also be reported in the eCRF. If the condition was present before entering the study, then it should be captured as medical history.
- Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers; intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs.

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).

- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures, and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB or Product Information for study drug, or marketed products, respectively, in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (via the AE and SAE eCRFs in the EDC) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

See Appendix E for the management of PHL cases.

9.4. Reporting of Serious Adverse Events

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

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 30 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during this period, and he/she considers the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further

information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

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

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

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

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event and Serious Adverse Event Forms in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form or Study Reference Manual for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. If a participant's treatment assignment is unblinded, the sponsor or its designee should be notified immediately for awareness.

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

9.7. Pregnancy

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

- The study drug must be discontinued immediately (female participants only; see Section 7.1 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form or Study Reference Manual.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

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

9.8. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. Product Complaints

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

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

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

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

9.10. Treatment of Overdose

There has been no clinical experience with overdose of INCB054707. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

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 INCB054707 15 mg, 45 mg, or 75 mg or placebo groups. The sample size calculation is based on Fisher exact test for the statistical comparison on the primary efficacy endpoint, proportion of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16. Based on the result from a Phase 2 trial of nemolizumab (Ständer et al 2020), the response rate is assumed to be 50% for the INCB054707 45 mg or 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 1 of the 3 active treatment groups and the placebo group.

10.2. Populations for Analysis

The populations for analysis are provided in Table 13.

Table 13: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
Safety	The safety population includes all participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
[redacted]	

10.3. Level of Significance

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

10.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1. Primary Analysis

The primary analysis will be based on the ITT population. The primary alternative hypothesis (superiority of the INCB054707 groups compared with the placebo group for the proportion of participants achieving ≥ 4-point improvement in Itch NRS score at Week 16) will be tested using exact logistic regression (Mehta and Patel 1995). This model will include the treatment groups and stratification factor. The unadjusted p-values between each of the INCB054707 groups and the placebo group will be compared with the prespecified significance level. Odds ratio and corresponding 95% CI will be provided as well. All nonresponders in the placebo-controlled period, as well as all participants who are missing postbaseline values, will be defined as nonresponders for the nonresponder imputation analysis. All participants who receive rescue therapy during the placebo-controlled period will be imputed as nonresponders.

The endpoint of different active doses versus placebo will be tested in a fixed sequence from high to low (75 mg, 45 mg, and 15 mg) at 2 sided $\alpha = 0.5$ level. The lower dose will be tested only if the statistical hypothesis associated with the higher dose is rejected.

10.4.2. Secondary Analysis

The secondary efficacy analyses will be conducted on the ITT population. All secondary efficacy variables will be summarized using descriptive statistics. For the binary endpoint, proportion of participants achieving IGA-TS (IGA score of 0 or 1 with a $\geq$ 2-grade improvement from baseline) at Week 16, summary statistics will include sample size, frequency, and percentages. For the time-to-event endpoint, time to $\geq$ 4-point improvement from baseline in Itch NRS score, 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).

10.4.3. Safety Analyses

The safety analyses will be conducted on the safety population. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug 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 to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v5.0 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship 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, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

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

[redacted]

[redacted]

[redacted]

[redacted]

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.

- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

The sponsor (or designee) will be responsible for:

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

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted], diary data), or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are in general all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records, electronic hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participants' files, and e-records/records kept at the pharmacy, at

the laboratories and at medico-technical departments involved in the clinical trial).

  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.

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

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

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

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

11.5. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

12. REFERENCES

Almeida TA, Rojo J, Nieto PM, et al. Tachykinins and tachykinin receptors: structure and activity relationships. Curr Med Chem 2004;11:2045-2081.

Andrassy KM. Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. Kidney Int. 2013;84:622-623.

Boozalis E, Tang O, Patel S, et al. Ethnic differences and comorbidities of 909 prurigo nodularis patients. J Am Acad Dermatol 2018;79:714-719.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

[redacted]

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2020.

Dazzi C, Erma D, Piccinno R, Veraldi S, Caccialanza M. Psychological factors involved in prurigo nodularis: a pilot study. J Dermatolog Treat 2011;22:211-214.

Elmariah S, Kim B, Berger T, et al. Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus. J Am Acad Dermatol 2021;84:747-760.

Ference JD, Last AR. Choosing topical corticosteroids. Am Fam Physician 2009;79:135-140.

[redacted]

Fukushi S, Yamasaki K, Aiba S. Nuclear localization of activated STAT6 and STAT3 in epidermis of prurigo nodularis. Br J Dermatol 2011;165:990-996.

[redacted]

Huang AH, Canner JK, Khanna R, Kang S, Kwatra SG. Real-world prevalence of prurigo nodularis and burden of associated diseases. J Invest Dermatol 2020;140:480-483.

[redacted]

Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. J Eur Acad Dermatol Venereol 2013;27:550-557.

INCB054707 Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Kowalski EH, Kneiber D, Valdenbran M, Patel U, Amber KT. Treatment-resistant prurigo nodularis: challenges and solutions. Clin Cosmet Investig Dermatol 2019;12:163-172.

Kwatra SG. Breaking the itch-scratch cycle in prurigo nodularis. N Engl J Med 2020;382:757-758.

McColl M, Boozalis E, Aguh C, et al. Pruritus in black skin: unique molecular characteristics and clinical features. J Natl Med Assoc 2021;113:30-38.

Mehta CR, Patel NR. Exact logistic regression: theory and examples. Stat Med 1995;14:2143-2160.

Millum J, Grady C. The ethics of placebo-controlled trials: methodological justifications. Contemp Clin Trials 2013;36:510-514.

Pereira MP, Steinke S, Zeidler C, et al. European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. J Eur Acad Dermatol Venereol 2018;32:1059-1065.

Perez GL, Peters MS, Reda AM, Butterfield JH, Peterson EA, Leiferman KM. Mast cells, neutrophils, and eosinophils in prurigo nodularis. Arch Dermatol 1993;129:861-865.

[redacted]

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

Todberg T, Zachariae C, Skov L. Treatment and burden of disease in a cohort of patients with prurigo nodularis: a survey-based study. Acta Derm Venereol 2020;100:adv00119.

Tsianakas A, Zeidler C, Ständer S. Prurigo nodularis management. Curr Probl Dermatol 2016;50:94-101.

Wang F, Kim BS. Itch: a paradigm of neuroimmune crosstalk. Immunity 2020;52:753-766.

[redacted]

Williams KA, Huang AH, Belzberg M, Kwatra SG. Prurigo nodularis: pathogenesis and management. J Am Acad Dermatol 2020;83:1567-1575.

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.

Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. Dermatol Clin 2018;35:189-197.

[redacted]

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP
The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[d] – oral – intravaginal – transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation[d] – oral – injectable – implantable[e] • Intrauterine device[e] • Intrauterine hormone-releasing system[e] • Bilateral tubal occlusion[e] • Vasectomized partner[e,f] • Sexual abstinence[c]

HRT = hormone replacement therapy.

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

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

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

[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.

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

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

Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Number of Study Participants

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

Study Visits

Remote Site Visit Guidelines:

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

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video calls). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible, in addition to the mandatory on-site visits outlined below.
- No efficacy assessments can be performed via telemedicine (video call, phone call, or via photography).
- Laboratory sampling: in order to support investigator oversight of participant safety and disease management, off-site laboratory sampling (in accordance with the SoA, see Table 3 and Table 4) may be allowed in 1 of 2 ways:
  - Use of home nursing services
  - Instruction of the participant to undergo some laboratory tests at a local (nearby) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed at certified laboratories and copies of results provided to the site.

Mandatory On-Site Visits:

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

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

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

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

- Screening
- Day 1 (Baseline)
- Week 4 visit
- Week 16 visit

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

- Week 24 visit
- Week 40 visit

Investigational Medicinal Product Dispensation and Distribution

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

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

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

Clinical Trial Monitoring

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

If the study site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Other Considerations

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

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

Reimbursement of Extraordinary Expenses

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

APPENDIX C. LIST OF STRONG/MODERATE SYSTEMIC CYP3A4 INHIBITORS AND STRONG SYSTEMIC CYP3A4 INDUCERS

Strong and Moderate Systemic CYP3A4 Inhibitors	Strong Systemic CYP3A4 Inducers
• Erythromycin • Troleandomycin, Clarithromycin, Telithromycin • Ciprofloxacin • Ketoconazole, Fluconazole, Itraconazole, Voriconazole, Posaconazole • Nefazodone • Diltiazem • Mibefradil • Verapamil • Aprepitant, Casopitant • Grapefruit/grapefruit juice • Seville oranges • Indinavir, Atazanavir, Nelfinavir, Ritonavir, Saquinavir, Boceprevir, Danoprevir, Elvitegravir, Lopinavir, Paritaprevir, Saquinavir, Telaprevir, Tipranavir, Ombitasvir, Cobicistat • Idelalisib • Conivaptan • Crizotinib • Cyclosporine • Dronedarone • Fluvoxamine • Imatinib • Tofisopam	• Rifampicin/rifampin • St John's wort • Phenytoin • Apalutamide • Carbamazepine • Bosentan • Efavirenz • Etravirine • Enzalutamide • Mitotane • Phenobarbital • Primidone

Note: Updated lists of CYP3A4 inhibitors/inducers can be found at Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

APPENDIX D. INSTRUCTION TO PARTICIPANTS FOR HANDLING INCB054707

The participant must be instructed in the handling of study drug as follows:

- Store study drug at room temperature (15°C-30°C/59°F-86°F).
- Keep study drug in a safe place and out of reach of children.
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets.
- Take study drug, preferably in the morning, with a full glass of water, without regard to food. Withhold drug self-administration for visits when the dose will be taken at the study site.
- If vomiting occurs after taking study drug, do not take another dose. If vomiting is persistent, contact the study site.
- Bring all used and unused study drug kits to the study site at each visit.
- If a dose is missed within the morning period, it is acceptable to take the dose within the same day (afternoon or evening). The next scheduled dose should occur at the usual time in the morning, unless required otherwise.

APPENDIX E. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has NOT had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 6.5.

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have the participant interrupt study drug.
- Notify the Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for PHL are met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gallbladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have the participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have the participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	12 JUL 2021
Amendment 2	06 MAY 2022

Amendment 2 (06 MAY 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to remove the interim analysis, modify exclusion criteria associated with estimated glomerular filtration rate; to add clarification on the types of PN lesions being assessed; and to add clarification on the management of creatine kinase elevations. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criteria #5 and #6); Section 8.2.2 Investigator's Global Assessment (Table 11: Investigator's Global Assessment)**

   Description of change: Revised wording from nodule to pruriginous lesion to be in line with chronic prurigo IGA.

   Rationale for change: To clarify that different types of pruriginous lesions are considered for this study

2. **Section 1, Protocol Summary (Treatment Groups and Duration); Section 4.1, Overall Design; Section 6.5.2, Criteria for Permanent Discontinuation of Study Drug; Section 6.6.4, Rescue Therapy; Section 7.1.1, Reason for Discontinuation**

   Description of change: Revised wording to indicate the use of rescue medication is allowable at any time during the study in participants who have substantial worsening of PN from baseline, but should be delayed if possible for at least 8 weeks after the first dose of study drug.

   Rationale for change: To clarify that administration of rescue therapy before Week 4 does not lead to discontinuation from study treatment.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Placebo-Controlled Period)**

   Description of change: Added a weight assessment to the screening visit.

   Rational for change: Weight is required for calculating the estimated glomerular filtration rate.

4. **Section 5.1, Inclusion Criteria (Criterion #3)**

   Description of change: Added a note that diagnosis may be based on investigator assessment and study participant interview.

   Rationale for change: To clarify that clinical diagnosis of PN may be based on investigator assessment and participant interview.

5. **Section 5.1, Inclusion Criteria (Criterion #4)**

   Description of change: Added a note to include over-the-counter products for PN therapy.

   Rationale for change: To clarify that over-the-counter products are acceptable.

6. **Section 5.1, Inclusion Criteria (Criteria #5 and #6); Section 8.2.2 Investigator's Global Assessment**

   Description of change: Added that pruriginous lesions may include nodules, papules, plaques, umbilicated ulcers, or ulcers.

   Rationale for change: To align with current literature and to clarify assessments to be used.

7. **Section 5.2, Exclusion Criteria (Criterion #13)**

   Description of change: Revised prior treatment with a JAK inhibitor to include a history of treatment failure (as assessed by the investigator through study participant interview) for PN or any other inflammatory condition with any systemic or topical JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib).

   Rationale for change: To clarify the previously failed treatments that exclude participation in the study.

8. **Section 5.2, Exclusion Criteria (Table 7: Exclusionary Laboratory Values [Criterion j])**

   Description of change: Modified estimated glomerular filtration rate from ≤ 70 mL/min based on Cockcroft-Gault formula to ≤ 45mL/min.

   Rationale for change: To align the exclusionary criteria with chronic kidney disease guidelines (Andrassy 2013).

9. **Section 5.2, Exclusion Criteria (Table 7: Exclusionary Laboratory Values [Criteria l and m])**

   Description of change: Added a note to the exclusion criteria laboratory values for PT and INR that the investigator may determine if the result is acceptable based on clinical assessment.

   Rationale for change: To allow the investigator to consider participation by clinical assessment in addition to the PT and/or INR values.

10. **Section 6.5.1 Criteria and Procedures for Dose Interruptions of Study Drug (Table 10: Guidelines for Interruption, Restart, and Discontinuation of Study Drug)**

    Description of change: Added guidance to describe management of creatine kinase elevations.

    Rationale for change: To clarify how creatine kinase elevations should be managed by investigators.

11. **Section 8.4.5, Laboratory Assessments (Table 12: Required Laboratory Analytes)**

    Description of change: Added the analysis of eGFR under Blood Chemistries.

    Rationale for change: To monitor in line with chronic kidney disease guidelines (Andrassy 2013).

12. **Section 10.3, Level of Significance; Section 10.4.1, Primary Analysis**

    Description of change: Updated the level of significance wording and revised the 2 sided $\alpha = 0.049$ level to 2 sided $\alpha = 0.5$ in alignment with removal of the interim analysis section.

    Rationale for change: To align with removal of the interim analysis.

13. **Section 10.5, Interim Analysis**

    Description of change: Removed interim analysis.

    Rationale for change: An interim analysis is not needed due to emerging safety and efficacy data for INCB054707 in other indications.

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

Amendment 1 (12 JUL 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to change the inclusion criteria associated with minimum number of nodules, to include a substudy for itch and sleep monitoring assessment, and to revise the interim analysis. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria**

   Description of change: Changed the inclusion criteria for minimum number of nodules from 10 to 20.

   Rationale for change: To align the minimum nodule count with the range listed in the description of Grade 3 in Table 11.

2. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements)**

   Description of change: Added the name for the coordinating principal investigator.

   Rationale for change: To update the coordinating principal investigator field in the table.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Placebo-Controlled Period**

   Description of change: [redacted]

   Rationale for change: [redacted]

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Placebo-Controlled Period**

   Description of change: Added Follow-up phone call (eDiary compliance) to the table.

   Rationale for change: To coincide with the text in Section 8.3.1 of the Protocol.

5. **Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints)**

   Description of change: [redacted]

   Rationale for change: [redacted]

6. **Section 5.2, Exclusion Criteria (Table 7: Exclusionary Laboratory Values)**

   Description of change: Removed "Conjugated (direct) bilirubin" and ≥ 1.2 × ULN from Exclusion Criterion 16g.

   Rationale for change: To clarify that Exclusion Criterion 16g is only applicable to total bilirubin.

7. **Section 6.5.1, Criteria and Procedures for Dose Interruptions of Study Drug (Table 10: Guidelines for Interruption, Restart, and Discontinuation of Study Drug)**

   Description of change: Added clarification for the number of times the study drug can be interrupted/restarted due to ALT and/or AST > 3.0 x ULN.

   Rationale for change: To clarify that the study drug can only be interrupted/restarted up to 2 times.

8. **Section 8.2.2, Investigator's Global Assessment (Table 11: Investigator's Global Assessment)**

   Description of change: Included appropriate literature reference and added description to Table 11 for each of the IGA grades.

   Rationale for change: To properly describe each of the IGA grades.

9. [redacted]

   Description of change: [redacted]

   Rationale for change: [redacted].

10. **Section 8.3.1.1, Itch NRS;** [redacted]

    Description of change: Clarified that the correct NRS ranges from 0 to 10.

    Rationale for change: To correct the NRS range.

11. [redacted]

12. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Placebo-Controlled Period; Table 4: Schedule of Activities for the Extension Period); Section 8.4.5, Laboratory Assessments (Table 12: Required Laboratory Analytes)**

    Description of change: [redacted]

    Rationale for change: [redacted]

13. **Section 10.3, Level of Significance**

    Description of change: Updated to include alpha spending and to show allocation of significance level for dose-response signal testing for interim and primary analyses.

    Rationale for change: To align with updates made to Section 10.5.

14. **Section 10.4.1, Primary Analysis**

    Description of change: Updated significance level for 2-sided test.

    Rationale for change: To align with updates made to Section 10.3 and Section 10.5.

15. **Section 10.5, Interim Analysis**

    Description of change: Updated number of participants required to perform interim analysis and added a 2-sided test for the presence of a dose-response signal.

    Rationale for change: To allow for efficacy testing during interim analysis.

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

Approval	[redacted] Approver [redacted] Biostatistics [redacted]
Approval	[redacted] Approver [redacted] Head of Inflammati [redacted]
Approval	[redacted] Approver [redacted] Clinical Research Scientist [redacted]
Approval	[redacted] Approver [redacted] Clinical Operations [redacted]
Approval	[redacted] Approver [redacted], Global Program Head [redacted]

Signature Page for VV-CLIN-013854 v5.0

Approval	[redacted] Approver [redacted] Biostatistics [redacted]
Approval	[redacted] Approver [redacted] Head of Inflammati [redacted]
Approval	[redacted] Approver [redacted] Clinical Research Scientist [redacted]
Approval	[redacted] Approver [redacted] Clinical Operations [redacted]
Approval	[redacted] Approver [redacted], Global Program Head [redacted]

Signature Page for VV-CLIN-013854 v5.0