

## **CLINICAL STUDY PROTOCOL**

**TITLE:** A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PLAQUE PSORIASIS

**IND No.:** 117780

**ClinicalTrials.gov ID:** NCT03343639

**Protocol No.:** MTI-109

**Protocol Version / Date:** Version 2.0 / 15-MAR-2018

**Development Phase:** Phase 2

**Sponsor:** Menlo Therapeutics Inc.  
200 Cardinal Way, 2<sup>nd</sup> Floor  
Redwood City, CA 94063  
USA

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**SIGNATURE PAGE FOR INVESTIGATOR(S)**

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I have read the protocol and agree to conduct this study in accordance with the protocol, all relevant laws and regulations in force at the time, International Conference on Harmonisation Guidelines for Good Clinical Practices, and the Declaration of Helsinki.

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Principal Investigator's printed name

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Principal Investigator's signature

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Date (DD-MMM-YYYY)

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**SPONSOR PROTOCOL APPROVAL SIGNATURE(S)**

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Approved by:

  
Chief Medical Officer

  
Signature

  
Date (DD-MMM-YYYY)

## PROTOCOL SYNOPSIS

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Pruritus in Adults with Plaque Psoriasis
Protocol Number:	MTI-109
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 2
Study Objectives:	<p>Primary objective: To assess the efficacy of serlopitant for the treatment of pruritus in adults with plaque psoriasis.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> <li>To assess the safety and tolerability of repeated oral doses of serlopitant in adults with plaque psoriasis.</li> <li>To assess the psychometric properties of Worst-Itch Numeric Rating Scale (WI-NRS).</li> </ul>
Study Design:	<p>This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with plaque psoriasis. Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 8 weeks. The study will be conducted at approximately 40 study sites in North America.</p> <p>The study will consist of three periods, for a total study period of approximately 12 or 14 weeks:</p> <ul style="list-style-type: none"> <li>Screening period: 2 or 4 weeks</li> <li>Treatment period: 8 weeks</li> <li>Follow-up period: 2 weeks</li> </ul> <p>During the screening period, subjects will undergo eligibility evaluation and will have their baseline symptom scores established. Subjects who require a washout of prior therapies per study criteria will perform their Screening visit 4 weeks prior to randomization. Subjects who do not require a washout of prior therapies can perform the Screening visit 2 weeks prior to randomization. Subjects must be willing and able to complete an electronic diary (eDiary) within a consistent timeframe on a daily basis, to wear actigraphy devices during sleep, and to comply with restrictions on allowable concomitant therapies for the duration of the study.</p> <p>At the Baseline visit, eligible subjects will be randomly assigned to receive serlopitant 5 mg or placebo. Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Study Day 1). Starting on Study Day 2, subjects will take one tablet per day orally. Serlopitant may be taken with or without food.</p> <p>The primary efficacy endpoint will be assessed at Week 8 of treatment.</p> <p>After completion of the treatment period or early discontinuation of study drug, all subjects will enter a 2 week follow-up period.</p>
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor blinded safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 200 subjects will be randomized.
Study Population:	The study will consist of adults with plaque psoriasis who have pruritus.

	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> <li>1. Male or female, age 18-80 years at consent.</li> <li>2. Diagnosis of plaque psoriasis for at least 6 months prior to randomization. <ol style="list-style-type: none"> <li>a. Presence of plaque psoriasis in any anatomic location, covering <math>\leq 10\%</math> BSA in total, at the Screening and Baseline visits.</li> </ol> </li> <li>3. Pruritus of at least 4 weeks' duration prior to the initial Screening visit, and throughout the screening period prior to randomization.</li> <li>4. Subjects must be willing to discontinue use of all psoriasis therapies other than the following, for the duration of the study: bland emollients (e.g., Cetaphil, Eucerin, Aquaphor) on any anatomic location; coal tar shampoos, limited to use on scalp.</li> <li>5. WI-NRS score <math>\geq 7</math> in the 24-hour period prior to the initial Screening visit.</li> <li>6. Average weekly WI-NRS score <math>\geq 6</math> for the two weeks immediately prior to randomization, as recorded in the eDiary.</li> <li>7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <math>&lt; 1\%</math> per year) from the time of the initial Screening visit until 2 weeks after last dose of study drug. Please refer to <a href="#">Section 7.1.5</a> of the protocol for acceptable methods of contraception.</li> <li>8. Weight <math>\geq 32</math> kg at the Screening and Baseline visits.</li> <li>9. Willing and able to complete daily eDiary entries within a consistent timeframe for the duration of the study. <ol style="list-style-type: none"> <li>a. Subjects must have <math>\geq 80\%</math> eDiary completion rate during the two weeks of the screening period immediately prior to randomization.</li> </ol> </li> </ol> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> <li>1. Prior treatment with serlopitant. <ol style="list-style-type: none"> <li>a. Prior treatment with other neurokinin-1 receptor (NK<sub>1</sub>-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) is not allowed within 1 year prior to randomization.</li> </ol> </li> <li>2. Clinical worsening of psoriasis in the opinion of the investigator (e.g., increase in affected BSA or severity requiring use of systemic psoriasis therapies) within 12 weeks prior to randomization.</li> <li>3. Predominance of non-plaque forms of psoriasis (e.g., guttate, drug-induced, pustular, erythrodermic).</li> <li>4. Presence of any concurrent medical condition which provides a clearly defined etiology for pruritus other than psoriasis. These include but are not limited to urticaria, atopic dermatitis or other dermatologic conditions, hepatic or renal disease, psychogenic pruritus, drug reaction, untreated hyperthyroidism, and infection.</li> <li>5. Treatment with systemic biologic therapies including but not limited to etanercept, infliximab, adalimumab, ustekinumab, secukinumab, or ixekizumab, within 6 months or 5 half-lives (whichever is longer) prior to randomization.</li> <li>6. Treatment with systemic non-biologic psoriasis therapies, including but not limited to systemic corticosteroids, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, cyclosporine, methotrexate, retinoids,</li> </ol>
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	<p>hydroxyurea, mycophenolate mofetil, thioguanine, sirolimus, azathioprine, or fumaric acid derivatives, within 12 weeks prior to randomization.</p> <p>7. Treatment with any of the following therapies within 4 weeks prior to randomization:</p> <ol style="list-style-type: none"> <li>Any topical/local psoriasis therapies other than those permitted per inclusion #4, including but not limited to topical corticosteroids, vitamin D analogues, calcineurin inhibitors, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, non-shampoo forms of coal tar, salicylates, retinoids, anthralin, or excimer laser. <ol style="list-style-type: none"> <li>Non-systemic corticosteroids that do not involve skin application (e.g., inhaled, intranasal, or intra-articular corticosteroids) will be permitted.</li> </ol> </li> <li>Phototherapy, with or without psoralen.</li> <li>Use of an indoor tanning facility, or sun exposure likely to result in sunburn.</li> <li>Systemic therapies with recognized anti-pruritic properties including but not limited to H1 antihistamines, doxepin, mirtazapine, gabapentin, pregabalin, cannabinoids, and kappa opioid receptor agonists.</li> <li>Any topical anti-pruritic therapies, including but not limited to H1 antihistamines, doxepin, capsaicin, or medicated emollients (e.g., menthol or pramoxine).</li> <li>Strong CYP3A4 inhibitors (see <a href="#">Appendix B</a> of the protocol).</li> </ol> <p>8. Treatment with any investigational therapy within 4 weeks or 5 half-lives (whichever is longer) prior to randomization.</p> <p>9. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) &gt; 2x the upper limit of normal (ULN) during screening.</p> <p>10. History of malignancy within 5 years prior to randomization, with the exception of completely treated and non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin.</p> <p>11. Presence of any of the following conditions meeting DSM-5 diagnostic criteria within 3 years prior to randomization: major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder, or other known psychiatric condition meeting DSM-5 diagnostic criteria which may confound the assessment of serlopitant safety or efficacy, compromise the safety of the subject, or interfere with the subject's ability to comply with protocol-mandated activities.</p> <p>12. Suicidal ideation within 3 years prior to randomization, or history of suicide attempt at any time.</p> <p>13. Known active hepatitis infection.</p> <p>14. Known history of human immunodeficiency virus (HIV) infection.</p> <p>15. Documented history of parasitic infection, including skin parasites such as scabies, within 12 months prior to randomization.</p> <p>16. History of hypersensitivity to serlopitant or any of its components.</p> <p>17. Currently pregnant or breastfeeding female subject.</p> <p>18. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of serlopitant safety or</p>
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	<p>efficacy, compromise the safety of the subject, or interfere with the subject's ability to comply with protocol-mandated activities; this includes any clinically significant screening ECG abnormalities and may include some clinically significant screening laboratory abnormalities.</p> <p>a. Unless specifically excluded per exclusion #9, clinically significant laboratory abnormalities at screening which are unlikely to interfere with the assessment of safety or efficacy in this trial, compromise the safety of the subject, or interfere with the subject's ability to comply with protocol-mandated activities are permitted.</p> <p>19. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g., extended international travel) during the subject's participation in the study.</p>
Study Drug:	Serlopitant 5 mg oral tablets and matching placebo.
Dosage:	<p>Serlopitant: 5 mg once daily by mouth for 8 weeks, following a 3-tablet loading dose on the first day of the treatment period.</p> <p>Matching placebo: Once daily by mouth for 8 weeks, following a 3-tablet loading dose on the first day of the treatment period.</p>
Primary Efficacy Endpoint:	The primary efficacy endpoint is the WI-NRS 4-point responder rate at Week 8.
Secondary Efficacy Endpoints:	<p>The key secondary efficacy endpoints are as follows:</p> <ul style="list-style-type: none"> <li>• WI-NRS 4-point responder rate at Week 4</li> <li>• Change in WI-NRS from baseline to Day 7</li> <li>• Change in WI-NRS from baseline to Day 3</li> </ul> <p>Additional secondary efficacy endpoints include the following:</p> <ul style="list-style-type: none"> <li>• Change in number of night-time scratching events from baseline to Week 8</li> <li>• Change in WI-NRS from baseline to Weeks 2, 4, 6, and 8</li> <li>• The WI-NRS 3-point responder rate at Weeks 4 and 8</li> <li>• Change in Static Patient Global Assessment of Itch Severity (sPGA)</li> <li>• Patient Global Impression of Change in Itch Severity (PGIC)</li> </ul>
Safety Endpoints:	<p>Safety endpoints include the following:</p> <ul style="list-style-type: none"> <li>• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)</li> <li>• Change in clinical laboratory parameters following study drug exposure</li> <li>• Changes in vital sign and electrocardiogram (ECG) parameters following study drug exposure</li> <li>• Plasma concentrations of serlopitant and metabolites</li> </ul>
Exploratory Endpoints:	<p>Exploratory endpoints include the following:</p> <ul style="list-style-type: none"> <li>• Change in Body Surface Area (BSA), and Physician Global Assessment (PGA) of psoriasis</li> <li>• Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – General</li> <li>• Change in Patient-Reported Outcomes Measurement Information System</li> </ul>

	<p>Itch Questionnaire (PIQ) score for Itch – Scratching Behavior</p> <ul style="list-style-type: none"> <li>• Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – Mood and Sleep</li> <li>• Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – Activity and Clothing</li> <li>• Change in sleep efficiency</li> <li>• Change in mean activity during the sleep period</li> </ul>
Decision Rule and Sample Size	<p>The decision rule is based on the Phase 2b screening methodology presented in Fleming and Richardson (<a href="#">Fleming 2004</a>). This two-category decision guideline compares the observed one-sided p-value for the primary endpoint to two categories: (0.025, 0.05) and (0, 0.025].</p> <ul style="list-style-type: none"> <li>• If the one-sided p-value is between 2.5% and 5% then the serlopitant-based regimen is plausibly efficacious and should be evaluated definitively in a subsequent Phase 3 clinical trial.</li> <li>• If the one-sided p-value is less than 2.5%, then the serlopitant-based regimen will have met the generally accepted level of evidence required to demonstrate efficacy.</li> </ul> <p>The sample size of 100 per group has been selected to achieve 90% power for the primary endpoint with</p> <ul style="list-style-type: none"> <li>• 5% one-sided alpha and responder rates of 24% (placebo) and 43.5% (serlopitant)</li> <li>• 2.5% one-sided alpha and responder rates of 24% (placebo) and 46% (serlopitant)</li> </ul> <p>Testing of the key secondary endpoints will take place should statistical significance be reached for the primary endpoint. Testing within the key secondary endpoints will be hierarchical with testing starting with the WI-NRS Week 4 responder rate, then the Day 7 WI-NRS endpoint, and finally the Day 3 WI-NRS endpoint.</p>
Statistical Methods:	<p>Primary efficacy analyses will be based upon an intent-to-treat (ITT) philosophy. The primary efficacy population will be the Full Analysis Set (FAS) which will include all randomized subjects who received at least one dose of study drug. Analyses performed on the Per Protocol (PP) population will be considered supportive. Subjects will be analyzed within the treatment group to which they are randomized.</p> <p>Efficacy Analyses:</p> <p>The primary efficacy endpoint is a binary variable taking on values of responder or non-responder. Subjects will be considered a responder if they have at least a 4-point reduction in WI-NRS between baseline and Week 8. Missing data imputation will be used for subjects who fail to complete the eDiary at Week 8. The primary endpoint will be summarized with descriptive statistics by treatment group and study week.</p> <p>The difference in the primary efficacy outcome measure between treatment groups will be tested using a Cochran Mantel Haenszel (CMH) test controlling for the stratification factors. The same test will be used for the Week 4 responder rates. Testing, using an analysis of covariance (ANCOVA) model, of the change in WI-NRS to Day 7 and Day 3 will be employed.</p>



	<p>Safety Analyses:</p> <p>The incidence of all adverse events (AEs) and treatment-related AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. An overview of AEs, which includes subject incidence of AEs, treatment-related AEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.</p> <p>Clinical safety laboratory values will be measured by a central laboratory. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Graphs of laboratory values over time will also be produced.</p> <p>Subjects with clinical laboratory values outside of the normal reference range at any post-baseline assessment will be summarized. Shifts from baseline laboratory values will be tabulated.</p> <p>The observed vital signs and ECG data and change from baseline for each measurement day will be summarized with descriptive statistics.</p>
Study Sites:	Approximately 40 study sites in North America.
Expected Duration of Subject's Participation	Approximately 12 or 14 weeks: 2 or 4 weeks of screening, 8 weeks of treatment, and a follow-up period of 2 weeks.

This study will be conducted in accordance with the Guidelines of Good Clinical Practices (GCPs).

## TABLE OF CONTENTS

SIGNATURE PAGE FOR INVESTIGATOR(S)	2
SPONSOR PROTOCOL APPROVAL SIGNATURE(S)	3
PROTOCOL SYNOPSIS	4
TABLE OF CONTENTS	10
LIST OF TABLES	13
LIST OF FIGURES	13
LIST OF APPENDICES	13
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	14
1 INTRODUCTION	16
1.1 Psoriasis and Pruritus	16
1.2 Current Treatment Options for Pruritus in the Setting of Psoriasis	16
1.3 Substance P and the Neurokinin-1 Receptor	17
1.4 Serlopitant	17
1.4.1 Serlopitant Background and Nonclinical Summary	17
1.4.2 Serlopitant Clinical Data in Phase 1 and Non-Pruritus Studies	18
1.4.3 Serlopitant in Pruritus-Related Studies	18
2 STUDY OBJECTIVES	20
3 STUDY DESIGN	20
3.1 Overall Study Design	20
3.2 Rationale for Study Design and Dose Selection	21
3.3 Study Endpoints	22
3.3.1 Primary Efficacy Endpoint	22
3.3.2 Key Secondary Efficacy Endpoints	22
3.3.3 Additional Secondary Efficacy Endpoints	22
3.3.4 Safety Endpoints	22
3.3.5 Exploratory Endpoints	23
3.4 Safety Review	23
3.4.1 Safety Monitoring Team	23
4 SELECTION OF STUDY POPULATION	23
4.1 Study Population	23
4.2 Inclusion Criteria	24
4.3 Exclusion Criteria	24
5 STUDY DRUG AND OTHER THERAPIES	26
5.1 Study Drug Supply, Route of Administration, and Storage	26
5.2 Labeling and Study Drug Accountability	27
5.3 Dosing Regimen	27
5.4 Dose Modification	27

5.5	Missed or Delayed Doses.....	27
5.6	Study Drug Discontinuation .....	27
5.7	Concomitant and Excluded Therapies .....	28
5.7.1	Allowed Therapies .....	28
5.7.2	Excluded Therapies and Study Restrictions .....	28
5.8	Assignment to Treatment.....	29
5.8.1	Randomization .....	29
5.8.2	Blinding.....	29
5.9	Treatment Compliance.....	30
6	<b>STUDY SCHEDULE AND ASSESSMENTS .....</b>	<b>30</b>
6.1	Efficacy Parameters .....	30
6.1.1	Itch Numeric Rating Scale.....	30
6.1.2	Actigraphy.....	30
6.1.3	Static Patient Global Assessment of Itch Severity.....	31
6.1.4	Patient Global Impression of Change in Itch Severity.....	31
6.1.5	Body Surface Area.....	31
6.1.6	Physician Global Assessment of Psoriasis.....	32
6.1.7	Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ).....	32
6.2	Safety Parameters.....	32
6.2.1	Vital Signs.....	33
6.2.2	Physical Examination.....	33
6.2.3	Clinical Laboratory Assessments.....	33
6.2.4	Electrocardiogram (ECG) .....	34
6.3	Pharmacokinetic Measurements .....	34
6.4	Subject Flow Diagram .....	34
6.5	Study Visits.....	35
6.5.1	Screening Visit/Period .....	35
6.5.2	Mid-Screening Telephone Contact .....	36
6.5.3	Baseline Visit.....	37
6.5.4	Week 1 Telephone Visit.....	38
6.5.5	Week 2 Visit .....	38
6.5.6	Week 4 Visit .....	38
6.5.7	Week 6 Telephone Visit.....	39
6.5.8	Week 8 Visit .....	40
6.5.9	Follow-up Visit.....	41
6.6	Early Termination .....	42
7	<b>ASSESSMENT OF SAFETY.....</b>	<b>42</b>

7.1	Definitions.....	42
7.1.1	Adverse Event.....	42
7.1.2	Serious Adverse Event.....	42
7.1.3	Abnormal Physical Exam, Laboratory, Vital Sign, and Electrocardiogram Findings.....	43
7.1.4	Deaths .....	44
7.1.5	Pregnancies and Contraception Requirements for Females.....	44
7.1.6	Worsening of Pruritus or Psoriasis .....	45
7.2	Methods and Timing for Recording and Reporting Adverse Events.....	45
7.2.1	Adverse Event Reporting Period .....	45
7.2.2	Eliciting Adverse Events.....	45
7.2.3	Assessment of Severity .....	46
7.2.4	Assessment of Causality .....	46
7.3	Follow-up of Adverse Events and Serious Adverse Events .....	47
7.4	Reporting Serious Adverse Events to the Sponsor and Institutional Review Board (IRB) or Ethics Committee (EC).....	47
7.5	Reporting Serious Adverse Events to Regulatory Authorities and Study Investigators.....	47
7.6	Emergency Unblinding.....	48
8	STATISTICAL METHODS.....	48
8.1	Decision Rule and Sample Size .....	48
8.2	Handling of Missing Data and Excluded Therapy Use .....	49
8.3	Analysis Populations.....	50
8.4	Subject Disposition.....	51
8.5	Subject Characteristics.....	51
8.6	Concomitant Medications .....	51
8.7	Treatment Compliance and Extent of Exposure .....	51
8.8	Efficacy Analyses .....	51
8.9	Sensitivity Analyses.....	52
8.9.1	Last Observation Carried Forward.....	52
8.10	Psychometric Analyses .....	52
8.11	Safety Analyses.....	53
8.11.1	Adverse Events .....	53
8.11.2	Clinical Safety Laboratory Results .....	53
8.11.3	Vital Signs.....	53
8.11.4	Electrocardiograms .....	53
8.11.5	Physical Exams .....	53
8.12	Pharmacokinetics Analysis .....	53
9	ADMINISTRATIVE ASPECTS .....	54

9.1	Changes to the Protocol .....	54
9.2	Study Termination .....	54
9.3	Monitoring and Auditing Procedures.....	54
9.4	Transfer of Obligations .....	54
9.5	Informed Consent.....	55
9.6	Communication with the Institutional Review Board .....	55
9.7	Disclosure and Confidentiality .....	55
9.8	Records and Electronic Case Report Forms .....	55
9.9	Good Clinical Practices and Ethical Study Conduct.....	56
9.10	End of Study Notification .....	56
9.11	Publication of Results .....	56
9.12	Final Report .....	56
10	REFERENCES .....	57

## **LIST OF TABLES**

Table 1	Adverse Event Grading.....	46
Table 2	Schedule of Visit Activities .....	60
Table 3	Schedule of eDiary and Actigraphy Assessments .....	61

## **LIST OF FIGURES**

Figure 1	Subject Flow Diagram .....	35
----------	----------------------------	----

## **LIST OF APPENDICES**

Appendix A	Schedule of Activities and Assessments.....	60
Appendix B	List of Strong CYP3A4 Inhibitors .....	62
Appendix C	Patient-Reported Outcomes Measurement Information System Itch Questionnaire .....	63

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Abbreviation</b>	<b>Definition</b>
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
BSA	Body surface area
CMH	Cochran Mantel Haenszel
CYP	Cytochrome P450
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
FAS	Full analysis set
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web response system
LFC	Liquid filled capsule
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NKA	Neurokinin A
NKB	Neurokinin B
NK <sub>1</sub> -R	Neurokinin-1 receptor
NK-2	Neurokinin-2 receptor
NK-3	Neurokinin-3 receptor
NOAEL	No observed adverse effect level
NRS	Numeric rating scale
OAB	Overactive bladder
PGA	Physician Global Assessment
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics

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PP	Per protocol
PROMIS®	Patient-Reported Outcomes Measurement Information System
PIQ	Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ)
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
sPGA	Static Patient Global Assessment
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analog scale
WI-NRS	Worst-itch numeric rating scale

## **1 INTRODUCTION**

### **1.1 Psoriasis and Pruritus**

Psoriasis is a chronic, non-communicable, immune-mediated inflammatory disease affecting at least 100 million individuals worldwide (Boehncke 2015; “Global report on Psoriasis” 2016). The most common clinical variant is plaque psoriasis (also known as “psoriasis vulgaris”), which affects approximately 85–90% of all patients with psoriasis; this typically manifests as raised, well-demarcated erythematous skin plaques with adherent silvery scales, which are a result of a hyperproliferative epidermis with premature maturation of keratinocytes and parakeratosis (Nestle 2009). Next to scaling of the skin (reported by 92% of patients with plaque psoriasis), the most frequently reported symptom is itching (reported by 72–87%) (“Global report on Psoriasis” 2016). In a survey of over 3,400 U.S. patients with psoriasis, itching was consistently reported as the most influential factor in determining their perception of psoriasis severity (Lebwohl 2016). In addition, pruritus has been associated with reduced health care quality of life in psoriasis patients, including impaired sleep quality and reduced psychological well-being (Zhu 2014).

### **1.2 Current Treatment Options for Pruritus in the Setting of Psoriasis**

At present, there are no FDA-approved therapies specifically indicated for the treatment of psoriatic pruritus. Treatment of pruritus in patients with psoriasis has traditionally been directed toward resolution of the skin lesions, as disease remission is thought to be associated with pruritus relief. However, several reports suggest that there may be no clinically meaningful correlation between pruritus severity and psoriasis disease severity. In a study of 102 patients with plaque-type psoriasis, pruritus was found in 89% of patients; no significant correlation was found between disease severity and presence or intensity of pruritus (Reich 2010). More recently, Roblin et al (Roblin 2014) reported baseline data for 157 psoriatic patients enrolling for a clinical trial; these patients had mild to moderate psoriasis according to Investigator Global Assessment. Of these, 97% of patients had pruritus, with 34% reporting severe pruritus (VAS score of greater than 70 mm). These data suggest that even when adequate control of psoriasis lesions can be achieved, patients may continue to experience pruritus out of proportion to their visible disease burden.

Recommendations for available treatments directed specifically toward reduction of itch in psoriatic patients, beyond standard of care psoriasis therapies, include topical agents such as bland emollients, pramoxine, menthol or capsaicin; sedating antihistamines such as hydroxyzine; and antidepressants such doxepin or mirtazapine (Szepietowski 2016; Dawn 2006). However, with the exception of topical capsaicin (Ellis 1993) and oral mirtazapine (Hundley 2004), evidence regarding efficacy with these agents for treatment of psoriatic pruritus is limited. Use of capsaicin and/or mirtazapine may also be limited by safety issues; topical capsaicin should not be applied to broken skin, and the sedative properties of mirtazapine limit its use during waking hours.



### 1.3 Substance P and the Neurokinin-1 Receptor

Substance P (SP) is an undecapeptide that belongs to the tachykinin family of neuropeptides, a group that also includes neurokinin A (NKA) and neurokinin B (NKB) (Hökfelt 2001). SP has been implicated in a number of biological functions, both physiological and pathophysiological, including pruritus perception, vomiting reflex, pain perception, and immunomodulatory responses (Lotts 2014; Andoh 1998; Steinhoff 2014). The biological actions of SP are mediated by tachykinin receptors, which consist of seven hydrophobic transmembrane domains coupled to G-proteins. Three tachykinin receptors have been identified: the neurokinin-1 (NK-1), neurokinin-2 (NK-2), and neurokinin-3 (NK-3) receptors (Harrison 2001). The NK-1 receptor (NK<sub>1</sub>-R) in particular has been studied in great detail. NK<sub>1</sub>-R is the primary receptor for SP in the human body, and is found on multiple cell types, include central and peripheral neurons, keratinocytes, and mast cells.

NK<sub>1</sub>-R stimulation has been shown to be an important pathway for pruritus perception (Stander 2015). Inhibition of this pathway results in decreased pruritus and scratching reflexes in animal models (Akiyama 2015). Preceding the development of serlopitant for pruritus-related conditions, a commercially available NK<sub>1</sub>-R antagonist (aprepitant, Emend®) has been used as a therapy to decrease pruritus in patients with chronic pruritus due to etiologies such as cutaneous T-cell lymphoma (Duval 2009; Torres 2012; Booken 2011) and erlotinib-induced pruritus (Santini 2012; Gerber 2010). Additionally, in a study of 20 patients with chronic pruritus of various etiologies treated with aprepitant, 16/20 patients (80%) experienced a considerable reduction of itch intensity (Stander 2010).

Radioimmunoassay and immunohistochemical staining studies have demonstrated that biopsies of skin from psoriasis patients contain more neurons immunoreactive for SP, NKA and NK-2 receptors, as well as non-neuronal inflammatory cells positive for SP, NKA, and NK-1 and NK-2 receptors, compared with healthy controls; in addition, numbers of SP positive nerves in plaque-bearing skin are significantly correlated with pruritus intensity (Amatya 2011). These findings suggest a role for SP signaling in psoriasis and psoriatic pruritus, and are also consistent with the robust body of evidence indicating the key role of SP signaling through its primary receptor, NK<sub>1</sub>-R, in the transmission of itch across multiple disease states. (Crowe 1994; Santini 2012; Akiyama 2015; El-Nour 2006; Lotts 2014; Hon 2007; Ward 2004; Slattery 2011).

### 1.4 Serlopitant

#### 1.4.1 Serlopitant Background and Nonclinical Summary

Serlopitant is a small molecule, highly selective NK<sub>1</sub>-R antagonist that is administered orally and metabolized by CYP3A4, with a plasma half-life of 45–86 hours. It binds with high affinity to the human NK<sub>1</sub>-R with a dissociation constant ( $K_d$ ) of 46 pM; displacing SP binding with a half-maximal inhibition concentration ( $IC_{50}$ ) of 61 pM. Serlopitant is a potent functional antagonist of SP-induced inositol phosphate generation.

Serlopitant has been extensively studied in animal toxicology studies, including chronic toxicology and carcinogenicity studies. In non-clinical chronic toxicology studies in rats,

mice and dogs, treatment related findings of potential clinical significance included increased salivation, decreased body weight gain and food consumption, slight changes in hematology and serum biochemistry parameters, mild increases in liver weight and mild histomorphologic changes. The histomorphologic changes were seen only in rats (not in dogs or mice) and included: very slight ovarian interstitial cell hypertrophy, mammary gland and uterine and ovarian atrophy; decreased corpora lutea; increased histiocytes in lung and mesenteric lymph nodes; slight skeletal and cardiac muscle degeneration; slight increased hematopoiesis in bone marrow; and slight to moderate vacuolation in kidney tubules. These nonclinical findings occurred at systemic exposures exceeding those anticipated to provide efficacy of serlopitant for pruritus indications in humans (1 to 5 mg tablet daily). No cardiac lesions have been observed in dog toxicity studies up to 9 months in duration nor in a 3-month mouse range-finding study and 2-year mouse carcinogenicity study at exposure higher than the lowest level which caused cardiotoxicity in rats. The no observed adverse effect level (NOAEL) in rats for histomorphological changes in the reproductive tract, mammary gland and bone marrow provides a 2-fold margin for the maximum-targeted exposure (5 mg tablet daily). The rat NOAEL for histomorphological changes in muscle and kidney provides a 4-fold margin for the maximum-targeted exposure (5 mg tablet daily).

In summary, the nonclinical toxicity noted with serlopitant provides no contraindications to the continuation of clinical trials via the oral route. Findings in the developmental toxicity studies support inclusion of women of childbearing potential in clinical trials in accordance with the study protocol and local regulatory guidances.

#### **1.4.2            *Serlopitant Clinical Data in Phase 1 and Non-Pruritus Studies***

In humans, serlopitant has been administered to over 1000 individuals. Single doses up to 400 mg have been well tolerated in healthy young adult males and single doses up to 25 mg have been well tolerated in the elderly. Multiple doses of up to 50 mg a day for 4 weeks have been well tolerated in healthy young adult males, and a single (loading) dose of 15 mg followed by daily doses of 5 mg for 2 weeks have been well tolerated in elderly males and females. Multiple daily doses of 4 mg liquid filled capsule (LFC) (bioequivalent to 5 mg tablets) for 1 year have been well tolerated in adult males and females with overactive bladder (OAB). Plasma concentrations of serlopitant appear to increase in a dose-proportional fashion up to 35 mg in both young adult and elderly subjects (with no gender differences). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young adult and elderly subjects.

In a Phase 2 study examining treatment of OAB (Study P003), the most common AEs during the initial 8-week base period across all treatment groups were headache (5.7%), diarrhea (5.2%), urinary tract infection (4.7%), dry mouth (4.5%), nasopharyngitis (4.5%), upper respiratory tract infection (4.3%), fatigue (4.1%), dizziness (3.8%), back pain (2.9%), nausea (2.3%), and peripheral edema (2.2%).

#### **1.4.3            *Serlopitant in Pruritus-Related Studies***

Serlopitant has been evaluated in two completed Phase 2 studies of subjects with chronic pruritus (TCP-101 and TCP-102).

### TCP-101

TCP-101 was a double-blind, placebo-controlled, multi-center study that compared serlopitant 0.25 mg, 1 mg, or 5 mg vs. placebo for the treatment of chronic pruritus. A total of 257 adult subjects 18–65 years of age with chronic pruritus were randomized to receive one of the four dose groups in a 1:1:1:1 randomization. Subjects received a loading dose of 3 tablets on Day 1 and thereafter received 1 tablet per day for 6 weeks. The primary efficacy endpoint was itch severity as measured on a VAS, summarized as a percentage change from baseline.

Mean percent decreases from Baseline in VAS score were larger in the active-treatment groups versus placebo at every scheduled post-baseline study visit. Overall, the results were the most profound for the serlopitant 1 mg and 5 mg groups. For the percent change from Baseline in VAS pruritus scores (the primary efficacy variable), the Week 6 pairwise least squares mean difference compared to placebo was 5.8 mm, 13.2 mm, and 14.2 mm for serlopitant 0.25 mg, 1 mg, and 5 mg, respectively.

The frequency of TEAEs and study drug related AEs was higher in the serlopitant 1 mg and 5 mg groups compared to the serlopitant 0.25 mg group, and the frequency in all three treatment groups were higher than in the placebo group. The frequency of AEs leading to study drug discontinuation was comparable in the serlopitant 5 mg and placebo group and higher than in the serlopitant 0.25 mg and 1 mg groups. There was one SAE reported in the serlopitant 1 mg group (spontaneous abortion, considered not related). There were no deaths. The most common AEs in the serlopitant groups were diarrhea (6.2%, 1 mg group), upper respiratory tract infection (4.7%, 0.25 mg group), somnolence (4.7%, 5 mg group), nasopharyngitis (4.6%, 1 mg group), headache (4.7%, 5 mg group), urinary tract infection (3.1%, 5 mg group), dry mouth (3.1%, 1 mg group), nausea (3.1%, 1 mg group), arthralgia (3.1%, 0.25 mg group), musculoskeletal pain (3.1%, 1 mg group) and pruritus (3.1%, 1 mg group). The most common AEs in the placebo group were headache (6.3%), nasopharyngitis (3.2%), upper respiratory tract infection (3.2%), urinary tract infection (3.2%) and asthma (3.2%).

### TCP-102

TCP-102 was a randomized, double-blind, placebo-controlled multi-center study that evaluated serlopitant 5 mg vs. placebo for the treatment of prurigo nodularis. A total of 128 adult subjects 18–80 years of age with prurigo nodularis were randomized to receive serlopitant or placebo in a 1:1 randomization. Subjects received a loading dose of 3 tablets on Day 1 followed by 1 tablet per day for 8 weeks. The primary efficacy endpoint was the average VAS score as recorded at the study visits. Results at Week 4 and Week 8 were the primary timepoints.

Serlopitant 5 mg was superior to placebo for the reduction of pruritus as measured by change in average VAS from baseline. For the primary endpoint, change from baseline at Week 4 and Week 8 by repeated measures analysis, the decrease from baseline was significantly greater in the serlopitant group than the placebo group, with a mean difference (serlopitant minus placebo) of -1.0 at Week 4 and -1.7 at Week 8. The mean difference at Week 2 was also significant, -0.9. In a post-hoc analysis of the percentage of subjects who were 4-point

responders on average VAS at Week 8, 25.0% of placebo subjects and 54.4% of serlopitant subjects were 4-point responders.

TEAEs were reported for 71.9% of serlopitant-treated subjects and 61.9% of placebo-treated subjects. The most frequently reported TEAEs in the serlopitant group were nasopharyngitis (17.2% serlopitant, 3.2% placebo), diarrhea (10.9% serlopitant, 4.8% placebo), and fatigue (9.4% serlopitant, 6.3% placebo). Treatment-related TEAEs were reported for 48.4% of serlopitant-treated subjects and 34.9% of placebo-treated subjects. The most frequently reported treatment-related TEAEs in the serlopitant group were fatigue (7.8%) and diarrhea, peripheral edema, dizziness, and headache (each 6.3%). Most TEAEs were mild or moderate; severe TEAEs were reported for 9.4% of serlopitant-treated subjects and 4.8% of placebo-treated subjects. There were no deaths during the study. Five subjects (3 serlopitant, 2 placebo) had SAEs. The SAEs were actinic elastosis, depression, dizziness, and vertigo in the serlopitant group; and bradycardia, syncope, respiratory failure, and neurodermatitis in the placebo group. Nine subjects (3 serlopitant, 6 placebo) discontinued due to TEAEs.

No clinically relevant changes were observed in chemistry, hematology, vital signs, or electrocardiogram (ECG) results.

The results of the Phase 2 studies in prurigo nodularis and chronic pruritus, together with the extensive safety experience with serlopitant to date and the scientific rationale for NK<sub>1</sub>-R inhibition in the treatment of pruritus associated with psoriasis, serve to support the evaluation of serlopitant for the treatment of pruritus in patients with psoriasis.

Please refer to the Investigator's Brochure for further information regarding serlopitant.

## **2 STUDY OBJECTIVES**

The primary objective of this study is to assess the efficacy of serlopitant for the treatment of pruritus in adults with plaque psoriasis.

The secondary objectives of this study are as follows:

- To assess the safety and tolerability of repeated oral doses of serlopitant in adults with plaque psoriasis.
- To assess the psychometric properties of Worst-Itch Numeric Rating Scale (WI-NRS).

## **3 STUDY DESIGN**

### **3.1 Overall Study Design**

This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with plaque psoriasis. Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily

oral doses of serlopitant 5 mg or placebo for 8 weeks. The study will be conducted at approximately 40 study sites in North America.

The study will consist of three periods, for a total study period of approximately 12 or 14 weeks:

- Screening period: 2 or 4 weeks
- Treatment period: 8 weeks
- Follow-up period: 2 weeks

During the screening period, subjects will undergo eligibility evaluation and will have their baseline symptom scores established. Subjects who require a washout of prior therapies per study criteria will perform their Screening visit 4 weeks prior to randomization. Subjects who do not require a washout of prior therapies can perform the Screening visit 2 weeks prior to randomization. Subjects will be provided an electronic diary (eDiary) at screening and are expected to complete the diary daily for the duration of the study. Subjects must be willing and able to complete the electronic diary within a consistent timeframe on a daily basis, to wear actigraphy devices during sleep, and to comply with restrictions on allowable concomitant therapies for the duration of the study.

At the Baseline visit (Day 1), eligible subjects will be randomly assigned to receive serlopitant 5 mg or placebo. Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Day 1). Starting on Study Day 2, subjects will take one tablet per day taken orally. Serlopitant may be taken with or without food.

The primary efficacy endpoint will be assessed at Week 8 of treatment.

After completion of the treatment period or early discontinuation of study drug, all subjects will enter a 2 week follow-up period.

### **3.2 Rationale for Study Design and Dose Selection**

In the TCP-102 study in patients with prurigo nodularis, serlopitant 5 mg taken daily for 8 weeks was superior to placebo for the reduction of pruritus, in both the overall study population as well as the subgroup of subjects with an atopic diathesis. Similarly, in the TCP-101 study in patients with chronic pruritus, serlopitant 5 mg and 1 mg taken daily for 6 weeks were superior to placebo for the reduction of pruritus, in both the overall study population and the subgroup of subjects with an atopic diathesis.

In both the TCP-102 and TCP-101 studies, serlopitant was generally well-tolerated and demonstrated an overall favorable safety profile at the doses evaluated.

The current MTI-109 study is designed to investigate the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in patients with psoriasis. The serlopitant 5 mg dose was selected for this study based on the following factors:

- The favorable efficacy, safety, and tolerability profile of serlopitant at the 5 mg dose level, as demonstrated in the TCP-102 and TCP-101 studies. These data are supported by safety experience across the serlopitant clinical development program. Over 250 subjects have been exposed to serlopitant at doses of 5 mg tablet equivalent daily for at least 6 weeks, and 41 subjects have been exposed for one year.
- Human CNS PET receptor occupancy (RO) data for serlopitant in healthy young males (Study P002) demonstrated that a serlopitant 5 mg LFC once daily dose is likely to achieve ~ 93% NK<sub>1</sub> RO at steady state. In previous dose-ranging experience with the NK<sub>1</sub>-R antagonist aprepitant, optimal clinical efficacy for the relief of chemotherapy-induced nausea and vomiting (CINV) was achieved at dose levels resulting in > 90% CNS NK<sub>1</sub> RO and preferably > 95% ([Chawla 2003](#); [Carstens 2010](#)).

### **3.3 Study Endpoints**

#### **3.3.1 Primary Efficacy Endpoint**

The primary efficacy endpoint is the WI-NRS 4-point responder rate at Week 8.

#### **3.3.2 Key Secondary Efficacy Endpoints**

The key secondary efficacy endpoints are as follows:

- The WI-NRS 4-point responder rate at Week 4
- Change in WI-NRS from baseline to Day 7
- Change in WI-NRS from baseline to Day 3

#### **3.3.3 Additional Secondary Efficacy Endpoints**

Additional secondary efficacy endpoints include the following:

- Change in number of night-time scratching events from baseline to Week 8
- Change in WI-NRS from baseline to Weeks 2, 4, 6 and 8
- The WI-NRS 3-point responder rate at Weeks 4 and 8
- Change in Static Patient Global Assessment of Itch Severity (sPGA)
- Patient Global Impression of Change in Itch Severity (PGIC)

#### **3.3.4 Safety Endpoints**

Safety endpoints include the following:

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Changes in clinical laboratory parameters following study drug exposure
- Changes in vital sign and ECG parameters following study drug exposure
- Plasma concentrations of serlopitant and metabolites

### **3.3.5            *Exploratory Endpoints***

Exploratory endpoints include the following:

- Change in Body Surface Area (BSA), and Physician Global Assessment (PGA) of psoriasis
- Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – General
- Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – Scratching Behavior
- Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – Mood and Sleep
- Change in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ) score for Itch – Activity and Clothing
- Change in sleep efficiency
- Change in mean activity during the sleep period

## **3.4                Safety Review**

### **3.4.1            *Safety Monitoring Team***

An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor blinded safety data on a regular basis throughout the study.

## **4                    SELECTION OF STUDY POPULATION**

### **4.1                Study Population**

The study will consist of approximately 200 adults with plaque psoriasis who have pruritus.

## **4.2 Inclusion Criteria**

Subjects must meet the following criteria to be randomized into the study:

1. Male or female, age 18–80 years at consent.
2. Diagnosis of plaque psoriasis for at least 6 months prior to randomization.
  - a. Presence of plaque psoriasis in any anatomic location, covering  $\leq 10\%$  BSA in total, at the Screening and Baseline visits.
3. Pruritus of at least 4 weeks' duration prior to the initial Screening visit, and throughout the screening period prior to randomization.
4. Subjects must be willing to discontinue use of all psoriasis therapies other than the following, for the duration of the study: bland emollients (e.g., Cetaphil, Eucerin, Aquaphor) on any anatomic location; coal tar shampoos, limited to use on scalp.
5. WI-NRS score  $\geq 7$  in the 24-hour period prior to the initial Screening visit.
6. Average weekly WI-NRS score  $\geq 6$  for the two weeks immediately prior to randomization, as recorded in the eDiary.
7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of  $< 1\%$  per year) from the time of the initial Screening visit until 2 weeks after last dose of study drug. Please refer to [Section 7.1.5](#) of the protocol for acceptable methods of contraception.
8. Weight  $\geq 32$  kg at the Screening and Baseline visits.
9. Willing and able to complete daily eDiary entries within a consistent timeframe for the duration of the study.
  - a. Subjects must have  $\geq 80\%$  eDiary completion rate during the two weeks of the screening period immediately prior to randomization.

## **4.3 Exclusion Criteria**

Subjects who meet any of the following criteria are not eligible for participation in the study:

1. Prior treatment with serlopitant.
  - a. Prior treatment with other neurokinin-1 receptor (NK<sub>1</sub>-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) is not allowed within 1 year prior to randomization.
2. Clinical worsening of psoriasis in the opinion of the investigator (e.g., increase in affected BSA or severity requiring use of systemic psoriasis therapies) within 12 weeks prior to randomization.
3. Predominance of non-plaque forms of psoriasis (e.g., guttate, drug-induced, pustular, erythrodermic).



4. Presence of any concurrent medical condition that provides a clearly defined etiology for pruritus other than psoriasis. These include but are not limited to urticaria, atopic dermatitis or other dermatologic conditions, hepatic or renal disease, psychogenic pruritus, drug reaction, untreated hyperthyroidism, and infection.
5. Treatment with systemic biologic therapies including but not limited to etanercept, infliximab, adalimumab, ustekinumab, secukinumab, or ixekizumab, within 6 months or 5 half-lives (whichever is longer) prior to randomization.
6. Treatment with systemic non-biologic psoriasis therapies, including but not limited to systemic corticosteroids, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, cyclosporine, methotrexate, retinoids, hydroxyurea, mycophenolate mofetil, thioguanine, sirolimus, azathioprine, or fumaric acid derivatives, within 12 weeks prior to randomization.
7. Treatment with any of the following therapies within 4 weeks prior to randomization:
  - a. Any topical/local psoriasis therapies other than those permitted per inclusion #4, including but not limited to topical corticosteroids, vitamin D analogues, calcineurin inhibitors, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, non-shampoo forms of coal tar, salicylates, retinoids, anthralin, or excimer laser.
    - i. Non-systemic corticosteroids that do not involve skin application (e.g., inhaled, intranasal, or intra-articular corticosteroids) will be permitted.
  - b. Phototherapy, with or without psoralen.
  - c. Use of an indoor tanning facility, or sun exposure likely to result in sunburn.
  - d. Systemic therapies with recognized anti-pruritic properties including but not limited to H1 antihistamines, doxepin, mirtazapine, gabapentin, pregabalin, cannabinoids, and kappa opioid receptor agonists.
  - e. Any topical anti-pruritic therapies, including but not limited to H1 antihistamines, doxepin, capsaicin, or medicated emollients (e.g., menthol or pramoxine).
  - f. Strong CYP3A4 inhibitors (see [Appendix B](#) of the protocol).
8. Treatment with any investigational therapy within 4 weeks or 5 half-lives (whichever is longer) prior to randomization.
9. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x the upper limit of normal (ULN) during screening.
10. History of malignancy within 5 years prior to randomization, with the exception of completely treated and non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin
11. Presence of any of the following conditions meeting DSM-5 diagnostic criteria within 3 years prior to randomization: major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder, or other known psychiatric condition meeting DSM-5 diagnostic criteria which may confound the assessment of serlopitant safety or efficacy, compromise the safety of the subject, or interfere with the subject's ability to comply with protocol-mandated activities.

12. Suicidal ideation within 3 years prior to randomization, or history of suicide attempt at any time.
13. Known active hepatitis infection.
14. Known history of human immunodeficiency virus (HIV) infection.
15. Documented history of parasitic infection, including skin parasites such as scabies, within 12 months prior to randomization.
16. History of hypersensitivity to serlopitant or any of its components.
17. Currently pregnant or breastfeeding female subject.
18. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of serlopitant safety or efficacy, compromise the safety of the subject, or interfere with the subject's ability to comply with protocol-mandated activities; this includes any clinically significant screening ECG abnormalities and may include some clinically significant screening laboratory abnormalities.
  - a. Unless specifically excluded per exclusion #9, clinically significant laboratory abnormalities at screening which are unlikely to interfere with the assessment of safety or efficacy in this trial, compromise the safety of the subject, or interfere with the subject's ability to comply with protocol-mandated activities are permitted.
19. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g., extended international travel) during the subject's participation in the study.

## **5 STUDY DRUG AND OTHER THERAPIES**

### **5.1 Study Drug Supply, Route of Administration, and Storage**

The study drug in this study is serlopitant 5 mg or placebo in a film-coated tablet formulation for oral administration. The serlopitant tablets contain microcrystalline cellulose, mannitol, croscarmellose sodium, silicon dioxide, sodium lauryl sulfate, and magnesium stearate, and are film coated with Opadry® Brown. The placebo tablets contain microcrystalline cellulose, lactose monohydrate, and magnesium stearate, and are film coated with Opadry® Brown.

The study drug will be provided in bottles that can be stored at room temperature (59–86°F, 15–30°C).

The tablets will be supplied in bottles, with 18 tablets per bottle. One bottle will be issued via Interactive Web Response System (IWRS) at baseline and at the Week 2 visit. Two bottles will be issued at the Week 4 visit. A total of 4 bottles will be dispensed to subjects completing 8 weeks of study drug treatment.

Additional details regarding study drug supplies can be found in the Pharmacy Manual.

## **5.2 Labeling and Study Drug Accountability**

The study drug will be appropriately packaged and labeled in bottles with 18 tablets per bottle. The study drug supplied for this study is not to be used for any purpose other than this study, and study drug accountability must be maintained for all bottles distributed to the investigative site.

Additional details regarding study drug labeling and accountability can be found in the Pharmacy Manual.

## **5.3 Dosing Regimen**

Subjects will take a loading dose (3 tablets orally) at the site on the first day of the treatment period (Study Day 1). Starting on Study Day 2, subjects will take one tablet per day orally. Subjects will be instructed to take all doses from Study Day 2 onward once a day. Serlopitant may be taken with or without food.

## **5.4 Dose Modification**

No dose modification of study drug will be allowed during this study.

## **5.5 Missed or Delayed Doses**

Each dose of study drug must be administered once daily and may be taken with or without food. If a dose is missed, that dose should be skipped, and the next dose should be taken the following day. The skipped dose will be considered and documented as a missed dose.

## **5.6 Study Drug Discontinuation**

Subjects should be discontinued from study drug treatment in the following situations:

- A female subject becomes pregnant
- The subject decides to discontinue study drug treatment, or withdraw consent from the study
- The subject receives a strong CYP3A4 inhibitor
- The subject receives an excluded medication for treatment of pruritus or psoriasis
- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion
- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion
- The subject experiences a NCI CTCAE Grade 3 or higher treatment emergent AE that is assessed as likely related to study drug

The Sponsor or designee should be contacted within 24 hours of investigator's awareness of any study drug treatment discontinuation. Investigators should make every effort to contact the Sponsor or designee before discontinuing study drug treatment, if possible.

Subjects who discontinue treatment with study drug prior to completing the treatment period will have a Follow-up visit 14 days after their last dose of study drug (see [Section 6.5.9](#)). Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued from study drug.

## **5.7 Concomitant and Excluded Therapies**

Concomitant therapies include any therapies (including over-the-counter medications) used by a subject from initiation of study drug treatment through the follow-up period. Medications/therapies for which discontinuation was required for the purposes of study participation (i.e., "washout medications/therapies") shall also be documented. A record of all medications used will be maintained for each subject throughout the study. Reported information will include a description of the type of drug, treatment period, dosing regimen, the route of administration, and drug indication.

### **5.7.1 Allowed Therapies**

Subjects using oral contraceptives, hormone-replacement therapy, or other maintenance therapies that are not Excluded Therapies ([Section 5.7.2](#)) may continue their use during the study.

Subjects will be allowed to use coal tar shampoos on scalp as medically indicated for the management of psoriasis throughout the study.

Bland emollient use started on or before the initial Screening visit should be continued during the study.

Treatment with non-systemic corticosteroids that do not involve skin application (e.g., inhaled, intranasal, ophthalmic, or intra-articular corticosteroids) will be allowed.

A record of all concomitant therapies will be maintained for each subject.

### **5.7.2 Excluded Therapies and Study Restrictions**

Therapy exclusions prior to the initial Screening visit are described in [Section 4.3](#). The following therapies and activities are excluded from the initial Screening visit through the follow-up period:

- NK<sub>1</sub>-R antagonists (other than study drug)
- Systemic biologic therapies, including but not limited to etanercept, infliximab, adalimumab, ustekinumab, secukinumab, or ixekizumab

- Systemic non-biologic psoriasis therapies, including but not limited to systemic corticosteroids, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, cyclosporine, methotrexate, retinoids, hydroxyurea, mycophenolate mofetil, thioguanine, sirolimus, azathioprine, or fumaric acid derivatives
- Topical/local psoriasis therapies other than those permitted per [Section 5.7.1](#), including but not limited to topical corticosteroids, vitamin D analogues, calcineurin inhibitors, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, non-shampoo forms of coal tar, salicylates, retinoids, anthralin, or excimer laser
- Phototherapy, with or without psoralen
- Use of an indoor tanning facility or excessive sun exposure/sunburn
- Systemic therapies with recognized anti-pruritic properties, including but not limited to H1 antihistamines, doxepin, mirtazapine, gabapentin, pregabalin, cannabinoids, and kappa opioid receptor agonists
- Topical anti-pruritic therapies, including but not limited to H1 antihistamines, doxepin, capsaicin, or medicated emollients (e.g., menthol or pramoxine)
- Strong CYP3A4 inhibitors (See [Appendix B](#))
- Any investigational therapy
- Initiation of any bland emollient use after the initial Screening visit

Use of any excluded therapies should be reported to the study medical monitor as soon as possible, and will be recorded as protocol deviations for subjects who receive them.

## **5.8 Assignment to Treatment**

### **5.8.1 Randomization**

Eligible subjects will be randomized to receive serlopitant 5 mg or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by the subject's reported WI-NRS score for the 24-hour period prior to the initial Screening visit (7-8, 9–10). An IWRS will be used to perform the randomization.

### **5.8.2 Blinding**

This study will be conducted as a double-blind study with the treatment assignment concealed from the subjects, the investigators and their staff, the Sponsor, and any designees of the Sponsor as required. The placebo will be formulated to be indistinguishable from the active study product(s). Study materials will be packaged and issued in a manner designed to maintain the blind for subjects and all study personnel involved in the direction and execution of study procedures, study assessments, and collection of data. The randomization code for each subject will be available to the sites for use only in an emergency situation. For

details of the procedure for unblinding of individual subjects in cases of emergency see [Section 7.6](#).

## **5.9 Treatment Compliance**

Records of study drug used, dosages administered, and intervals between visits will be kept during the study. Subjects will record in the eDiary the doses administered and whether a dose was taken within 2 hours of eating a meal. Subjects will be asked to return all partially used and empty bottles to the study site at each visit. The site staff will count and record the number of remaining tablets in each returned bottle. Compliance will be calculated based on tablet counts as recorded on the eCRF. The site staff will review the subject's eDiary to help evaluate compliance with dosing at each study visit. Discrepancies between compliance as assessed by tablet counts and doses recorded in the eDiary will be reconciled and documented at each visit. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

## **6 STUDY SCHEDULE AND ASSESSMENTS**

### **6.1 Efficacy Parameters**

#### **6.1.1 *Itch Numeric Rating Scale***

The Itch NRS is a validated, self-reported instrument for measurement of itch intensity ([Kimball 2016](#)). It uses a 24-hour recall period and asks subjects to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicate greater itch intensity. In this study, worst itch intensity (WI-NRS) during a 24-hour recall period will be captured. Subjects will record their Itch NRS scores once daily via eDiary at the same time each day (+/- 3 hours) throughout the screening, treatment, and follow-up periods, as outlined in [Appendix A](#). Subjects may be allowed to adjust the timing of eDiary completion within the first week of Screening as needed. Standardized training and instructions will be provided to all subjects prior to eDiary use.

#### **6.1.2 *Actigraphy***

High-resolution actigraphy is an objective method for quantifying nocturnal scratching events and sleep-related parameters using high resolution actigraphy devices on each wrist. The device weighs 16 g (0.56 oz) without the strap, and is made of medical device grade housing material. The device is water resistant up to 10 meters, dust-tight, and drop-resistant to 0.5 m. It is functional for operation between 41–104°F (5–40°C).

The assessment requires each subject to wear the actigraphy devices, which are the size of a medium size wrist watch, on each wrist at night (during sleep), with the option to wear them during the waking hours as well; if tolerated by the subject, keeping at least one watch on 24/7 would be expected to optimize data quality. It is strongly suggested that subjects wear the actigraphy devices for at least four consecutive nights within any given week; while intermittent breaks from wearing actigraphy devices due to temporary irritation or discomfort

are permitted, they should ideally be limited to a maximum of three consecutive nights per week throughout the study.

The devices will be programmed and activated prior to being provided to subjects. Once received, the subjects can simply put the devices on their wrists and they will record automatically. The devices are returned to the study site at each subsequent study visit where the data are downloaded and sent for analysis.

The 3-D acceleration data ( $\text{m/sec}^2$ ) from the actigraphy device is analyzed with a neural network that was developed to discriminate scratching from other nighttime events. The algorithm was developed and tested in a study of 24 subjects (6 healthy, 18 with atopic dermatitis) who were video recorded for one night in a sleep lab while wearing actigraphy devices on each wrist. The video recordings were scored to quantify the time and duration of each scratching event. A strong correlation was shown ( $r = 0.98$ ) between the number of scratching events per hour measured with the actigraphy analysis versus the video scoring. In contrast, subjective questionnaires completed by the subjects the following morning had a poor correlation with the true number of scratching events. For example, the best correlation was 0.6 with a VAS. The full description of the algorithm and the study has been submitted to *IEEE Journal of Biomedical and Health Informatics* (Moreau 2016).

Actigraphy measurements will be assessed as outlined in [Appendix A](#).

### **6.1.3            *Static Patient Global Assessment of Itch Severity***

The sPGA is designed to assess overall itch severity. Each subject is asked to rate the severity of his/her itchiness in the past 7 days on a 5-point scale as none, mild, moderate, severe, and very severe. The sPGA will be collected as outlined in [Appendix A](#).

### **6.1.4            *Patient Global Impression of Change in Itch Severity***

The PGIC in Itch Severity is a single item used to assess the change in overall itch severity since the Baseline visit. Each subject will rate the change in his/her itch severity on a 7-point scale from very much better, moderately better, a little better, no change, a little worse, moderately worse, to very much worse. PGIC will be collected as outlined in [Appendix A](#).

### **6.1.5            *Body Surface Area***

The BSA is used to assess the overall extent of plaque psoriasis at a given time point. The evaluator will measure the percentage (%) of skin covered with plaque psoriasis by the hand method. The hand method is commonly used for estimation with the assumption that 1 hand = 1% of the total body surface area. One hand is defined as the subject's palm to the proximal interphalangeal joint. For scoring, multiple small lesions must be "merged" to measure. Also if central clearing is noted, include only the affected area in calculation. The percent BSA involvement will be collected as outlined in [Appendix A](#). The same qualified evaluator should assess a subject across all study visits for BSA and PGA, when possible.

### **6.1.6 Physician Global Assessment of Psoriasis**

The PGA is the physician's determination of a patient's overall plaque psoriasis lesions at a given time point ("[Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis](#)" 2004). Overall, lesions are assessed for induration, erythema, and scaling on a scale ranging from clear (0), almost clear (1), mild (2), moderate (3), severe (4), to very severe (5). PGA scores will be assessed as outlined in [Appendix A](#). The same qualified evaluator should assess a subject across all study visits for BSA and PGA, when possible.

<b>Score</b>	<b>Grade</b>	<b>Definition</b>
<b>0</b>	<b>Clear</b>	No plaque elevation above normal skin level; may have residual nonerythematous discoloration; no psoriatic scale
<b>1</b>	<b>Almost Clear</b>	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale
<b>2</b>	<b>Mild</b>	Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
<b>3</b>	<b>Moderate</b>	Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered
<b>4</b>	<b>Severe</b>	Marked elevation with hard, sharp edges to plaque; severe erythema (red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
<b>5</b>	<b>Very Severe</b>	Very marked elevation with very hard, sharp edges to plaque; severe erythema (very red coloration); very coarse, very thick scales with virtually all lesions covered and a very rough surface

### **6.1.7 Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ)**

Patient-Reported Outcome Measurement Information System (PROMIS®) Itch Questionnaire (PIQ) is an itch-specific instrument that measures quality of life impairment related to itch in the previous week. The PIQ includes 4 domains (general, scratching behavior, mood and sleep, and activity and clothing) as noted in [Appendix C](#). Subjects will complete the PIQ short forms as outlined in [Appendix A](#).

## **6.2 Safety Parameters**

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); vital signs; physical examinations; clinical laboratory assessments; ECGs; pharmacokinetics (PK) measurements; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.



### **6.2.1 Vital Signs**

Vital signs will include measurements of heart rate, sitting blood pressure, respiration rate, and temperature after being seated for at least 5 minutes. Vital signs will be assessed as outlined in [Appendix A](#) and at unscheduled study visits when clinically indicated. The subjects' height and weight will be measured as outlined in [Appendix A](#).

### **6.2.2 Physical Examination**

Physical examinations will be performed as outlined in [Appendix A](#) and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the initial Screening visit, while subsequent examinations will be abbreviated and targeted to assessment of disease activity and/or subjects' symptoms.

### **6.2.3 Clinical Laboratory Assessments**

Samples for hematology, chemistry, urinalysis, urine pregnancy testing, serum pregnancy testing (when necessary), endocrine testing, and reproductive endocrine testing (when necessary) will be collected as outlined in [Appendix A](#) and at unscheduled study visits when clinically indicated. Samples will be analyzed at a central laboratory unless otherwise specified.

Detailed instructions regarding sample collection, preparation, and shipment can be found in the laboratory manual. Laboratory assessments will include the following:

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, ALT, AST, alkaline phosphatase, total bilirubin, LDH, uric acid, total protein, lipid panel
- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Urinalysis: color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen, microscopic analysis
- Endocrine: TSH, free T4, cortisol, corticotropin
- Reproductive endocrine (for all female subjects under 55 years of age at consent): serum FSH, LH, estradiol, progesterone, AMH

#### **6.2.4            *Electrocardiogram (ECG)***

A standard 12-lead ECG will be performed as outlined in [Appendix A](#) and at unscheduled study visits when clinically indicated and read centrally. Detailed instructions will be provided in the ECG manual.

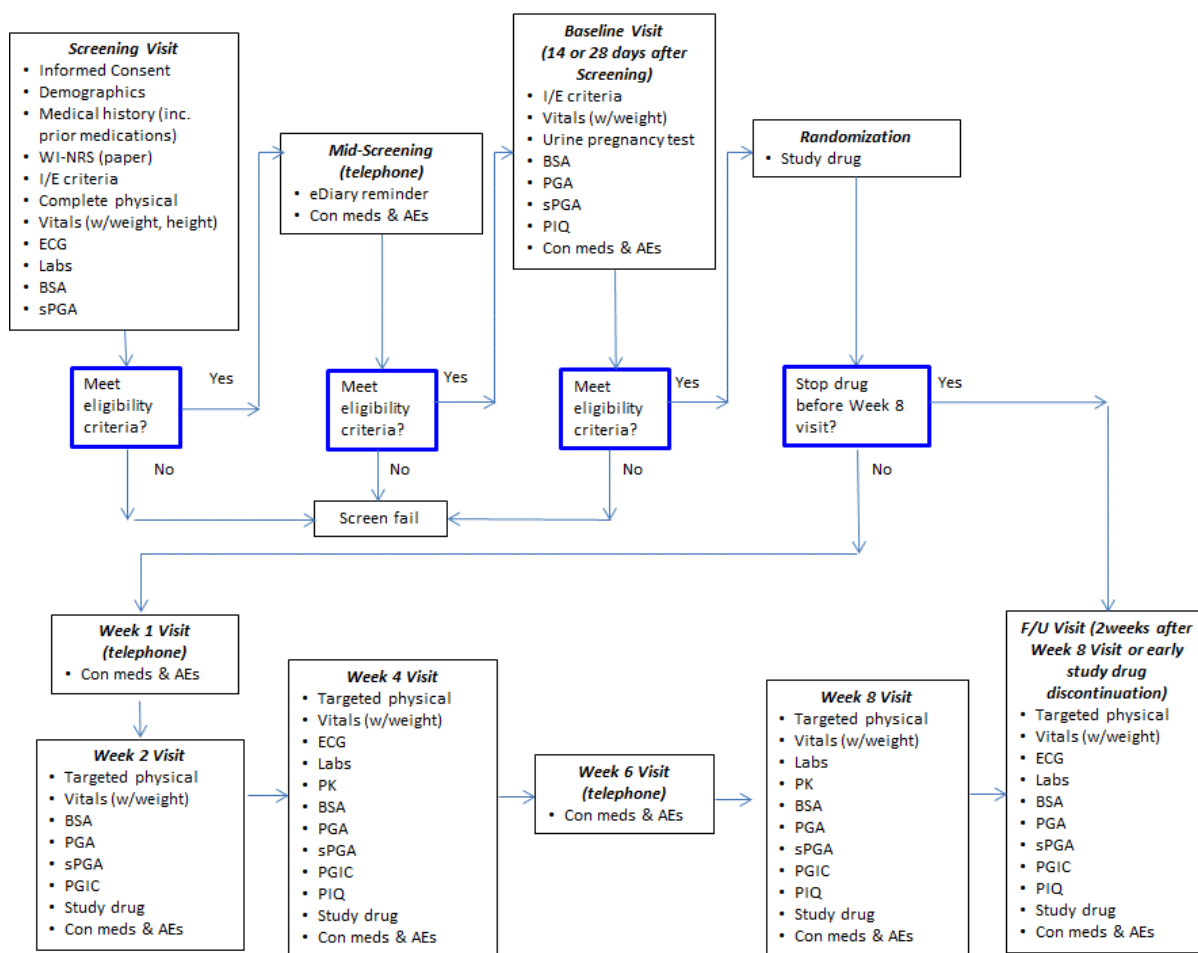
### **6.3                Pharmacokinetic Measurements**

Sparse PK sampling will be collected as outlined in [Appendix A](#). The date and time of dosing prior to PK sample collection will be confirmed by the site, and time of PK sample collection will be recorded in the eCRF. The plasma concentrations of serlopitant and metabolites will be determined and data used for population PK analysis. Detailed instructions regarding PK sample collection, preparation, and shipment can be found in the laboratory manual.

### **6.4                Subject Flow Diagram**

The visit schedule and assessments are summarized in [Appendix A](#). The following subject flow diagram provides a summary of assessments and decision points for each subject. The eDiary and actigraphy assessments are performed throughout the study and are not confined to scheduled visits. Refer to [Appendix A](#) for frequency and duration of these assessments.

**Figure 1 Subject Flow Diagram**



## 6.5 Study Visits

The following sections describe the procedures and assessments to be performed at each study visit. Details of each procedure and assessment can be found in [Sections 6.1 through 6.4](#). Subject self-assessments should be done prior to the physician assessments, when possible.

Unscheduled visits may be performed as necessary, and may include procedures or assessments as deemed necessary by the investigator.

The eDiary and actigraphy assessments are performed throughout the study and are not confined to scheduled visits. Refer to [Appendix A](#) for frequency and duration of these assessments.

### 6.5.1 Screening Visit/Period

Subjects who require a washout from prior therapies per study criteria will have their Screening period start 4 weeks prior to the Baseline visit. Subjects who do not require a

washout from prior therapies will have their Screening period start 2 weeks prior to the Baseline visit. The following screening procedures are to be performed at the Screening visit.

- Informed consent will occur prior to any protocol-mandated procedures, including the stopping of any excluded therapies
- Demographics
- Medical history (including prior medications)
- Worst-Itch Numeric Rating Scale (paper)
- Inclusion/exclusion criteria review
- Complete physical examination
- Vital signs (including height and weight)
- ECG
- Laboratory
  - Hematology
  - Chemistry
  - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
  - Urinalysis
  - Endocrine
  - Reproductive endocrine labs for females under 55 years of age at consent
- BSA
- sPGA
- After training, dispense eDiary with instructions to complete it every day during the Screening Period
- Dispense actigraphy watches with instructions to wear them every day during the Screening Period.
- Schedule the Baseline visit; A minimum of 14 opportunities to complete the WI-NRS in the eDiary are required prior to assessing eligibility.

#### **6.5.2            *Mid-Screening Telephone Contact***

Subjects who require a washout from prior therapies will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as

previously instructed at the Screening visit. During this telephone contact the following procedures are to be performed:

- Concomitant medications
- eDiary review and reminder, with re-training as required
- Confirm next scheduled visit date

### **6.5.3            *Baseline Visit***

The Baseline visit occurs 2 or 4 weeks (+ 3 days) after the Screening visit, depending on if a washout of prior therapies per study criteria was required. At the Baseline visit, the following procedures and assessments are to be performed:

- Inclusion/exclusion criteria review
- Concomitant medications
- Adverse events
- Vital signs (including weight)
- Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- BSA
- PGA
- sPGA
- PIQ
- Review eDiary compliance; retrain as needed
- Randomization if eligible
- Dispense study drug; subjects will take first dose while on site
- Collect and replace actigraphy watches
- Schedule future visits

All Baseline assessments must be performed and eligibility confirmed prior to randomization in the IWRS system. Randomized subjects will begin treatment with study drug at the site (i.e., 3 tablets loading dose) on Study Day 1.

#### **6.5.4            *Week 1 Telephone Visit***

The Week 1 visit is a telephone visit that occurs 7 days ( $\pm 3$  days) after the Baseline visit. At the Week 1 visit, the following procedures and assessments are to be performed:

- Concomitant medications
- Adverse events
- eDiary review, with re-training as required
- Confirm next scheduled visit date

#### **6.5.5            *Week 2 Visit***

The Week 2 visit occurs 14 days ( $\pm 2$  days) after the Baseline visit. At the Week 2 visit, the following procedures and assessments are to be performed:

- Concomitant medications
- Adverse events
- Targeted physical exam
- Vital signs (including weight)
- BSA
- PGA
- sPGA
- PGIC
- eDiary review, with re-training as required
- Study drug compliance with re-training as required
- Dispense study drug
- Collect and replace actigraphy watches
- Confirm next scheduled visit date

#### **6.5.6            *Week 4 Visit***

The Week 4 visit occurs 28 days ( $\pm 3$  days) after the Baseline visit. At the Week 4 visit, the following procedures and assessments are to be performed:

- Concomitant medications

- Adverse events
- Targeted physical exam
- Vital signs (including weight)
- ECG
- Laboratory
  - Hematology
  - Chemistry
  - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
  - Urinalysis
- PK blood sample collection
- BSA
- PGA
- sPGA
- PGIC
- PIQ
- eDiary review, with re-training as required
- Study drug compliance with re-training as required
- Dispense study drug
- Collect and replace actigraphy watches
- Confirm next scheduled visit date

#### **6.5.7            *Week 6 Telephone Visit***

The Week 6 visit is a telephone visit that occurs 42 days ( $\pm$  3 days) after the Baseline visit. At the Week 6 visit, the following procedures and assessments are to be performed:

- Concomitant medications
- Adverse events
- eDiary review, with re-training as required
- Confirm next scheduled visit date

### **6.5.8            *Week 8 Visit***

The Week 8 visit occurs 56 days ( $\pm$  3 days) after the Baseline visit. At the Week 8 visit, the following procedures and assessments are to be performed:

- Concomitant medications
- Adverse events
- Targeted physical exam
- Vital signs (including weight)
- Laboratory
  - Hematology
  - Chemistry
  - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
  - Urinalysis
  - Endocrine
  - Reproductive endocrine labs for females for females under 55 years of age at consent
- PK blood sample collection
- BSA
- PGA
- sPGA
- PGIC
- PIQ
- eDiary review, with re-training as required
- Study drug compliance
- Collect study drug
- Collect and replace actigraphy watches
- Confirm Follow-up visit date



### **6.5.9            *Follow-up Visit***

For all subjects, the Follow-up visit occurs 14 days (+ 3 days) after the Week 8 visit or the last dose of study drug for subjects who discontinue study drug early. Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued study drug early. At the Follow-up visit, the following procedures and assessments are to be performed:

- Concomitant medications
- Adverse events
- Targeted physical exam
- Vital signs (including weight)
- ECG
- Laboratory
  - Hematology
  - Chemistry
  - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
  - Urinalysis
  - Endocrine
  - Reproductive endocrine labs for females for females under 55 years of age at consent
- BSA
- PGA
- sPGA
- PGIC
- PIQ
- eDiary review
- Study drug compliance (if not previously performed for subjects who discontinued study drug early)
- Collect study drug (if not previously performed for subjects who discontinued study drug early)
- Collect eDiary and actigraphy watches

## **6.6 Early Termination**

Early termination of a subject from the study may occur due to the following reasons:

- lost to follow-up
- withdrawal of consent by the subject

In accordance with legal requirements and International Conference on Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If a subject is willing to provide a reason for withdrawal, this will be recorded in the electronic Case Report Form (eCRF). The Investigator or site staff must make every effort to contact subjects who are suspected of being lost to follow-up. A minimum of two attempted telephone contacts and a certified letter are required before a subject can be deemed as lost to follow-up. Attempts to contact such subjects must be documented in the subject's source documents.

## **7 ASSESSMENT OF SAFETY**

### **7.1 Definitions**

#### **7.1.1 *Adverse Event***

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

AEs include treatment emergent exacerbations of pre-existing illnesses and AEs that occur as a result of protocol-mandated interventions.

#### **7.1.2 *Serious Adverse Event***

An SAE is considered “serious” if it results in any of the following outcomes:

- Death
- Life-threatening AE (i.e. the subject was at immediate risk of death from the event as it occurred. An event that might have led to death if it had occurred with greater severity is not “life-threatening”)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/ birth defect
- Important medical event (i.e. an event that may not result in death, be life-threatening, or require hospitalization, but which may be considered serious by the investigator or Sponsor, as it may jeopardize the subject and may require medical/surgical intervention to prevent one of the outcomes listed above). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following are not considered SAEs: a visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event), an elective surgery planned prior to signing consent, admission as per protocol for planned medical/surgical procedure, and/or routine health assessments requiring admission for baseline/trending of health status (e.g., routine colonoscopy).

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., mild, moderate, or severe pain); the event itself may be of minor medical significance (e.g., severe back pain). “Serious” is a regulatory definition, as defined above. Seriousness (not severity) serves as the basis for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

### **7.1.3            *Abnormal Physical Exam, Laboratory, Vital Sign, and Electrocardiogram Findings***

Abnormal physical exam findings that are clinically significant and are identified prior to the first dose of study drug should be recorded as medical history. New or worsening clinically significant abnormal physical exam findings identified after the first dose of study drug should be recorded as AEs.

Only abnormal laboratory, vital sign, and ECG findings that are considered clinically significant by the investigator (e.g., require active management or are associated with accompanying symptoms/signs) will be recorded as medical history or AEs on the eCRF. Abnormal laboratory, vital sign, and ECG findings that occur prior to the first dose of study drug should be recorded as medical history, and abnormal findings that occur after the first dose of study drug should be recorded as AEs.

If the clinically significant laboratory, vital sign, or ECG abnormality is a sign associated with a confirmed disease or condition (e.g., elevated creatinine in a subject diagnosed with chronic kidney disease), only the diagnosis (chronic kidney disease) needs to be recorded on the AE eCRF.

Separate instances of the same clinically significant laboratory, vital sign, or ECG abnormality across visits should not be recorded as separate AEs or SAEs.

#### **7.1.4 Deaths**

Any deaths that occur from the time of informed consent to the Follow-up visit, regardless of attribution, must be reported within 24 hours of investigator's awareness of the death. See *MTI-109 SAE Report Form and Pregnancy Report Form Completion Guidelines* for complete instructions.

The Sponsor should be provided a copy of any post-mortem findings and/or relevant medical reports, including histopathology.

#### **7.1.5 Pregnancies and Contraception Requirements for Females**

For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female; in the absence of 12 months of amenorrhea, a single FSH measurement is not sufficient evidence of postmenopausal status.

For the purposes of this study, acceptable contraception is defined below based on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: ICH M3(R2) dated January 2010, and other available guidelines ([“U.S. Medical Eligibility Criteria for Contraceptive Use, 2010” 2010](#); [“Recommendations related to contraception and pregnancy testing in clinical trials” 2014](#); [“M3\(R2\) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” 2010](#)):

All female subjects of childbearing potential must use highly effective contraception, which includes the use of one or more of the following acceptable methods:

1. Surgical sterilization (e.g., bilateral tubal occlusion or ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
2. Total (as opposed to periodic or cyclic) abstinence from heterosexual intercourse
3. Hormonal contraception associated with consistent inhibition of ovulation; these may include (but are not necessarily limited to) oral, intravaginal, implantable, injectable, or transdermal delivery methods.
  - a. Progesterone only oral contraceptives are excluded as a highly effective method, as they do not consistently inhibit ovulation.
4. Intrauterine device/systems
5. Exclusive monogamous heterosexual intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner

Any pregnancy occurring in a female subject or the female partner of a male subject, from the first study drug administration through the Follow-up visit must be reported within

24 hours of the investigator's awareness of the pregnancy. See *MTI-109 SAE Report Form and Pregnancy Report Form Completion Guidelines* for complete instructions.

The investigator will follow the pregnancy to delivery or other pregnancy outcome.

Pregnancy in a female clinical trial subject or female partner of a male clinical trial subject is not an SAE per se. Complications of such pregnancies (for example, spontaneous abortion) may qualify as SAEs and should be reported as such even if they occur after the Follow-up visit. Any congenital anomalies/birth defects must be recorded and reported as SAEs. See *MTI-109 SAE Report Form and Pregnancy Report Form Completion Guidelines* for complete instructions.

### **7.1.6 Worsening of Pruritus or Psoriasis**

Pruritus or psoriasis should be recorded as an AE or SAE only if considered by the investigator to have unexpectedly worsened in severity or worsened beyond the subject's normal fluctuations during the study. It is important to include a description of the nature of the unexpected worsening when recording the AE or SAE (e.g., new psoriasis lesions in previously uninvolved skin or pruritus requiring use of excluded therapy).

## **7.2 Methods and Timing for Recording and Reporting Adverse Events**

### **7.2.1 Adverse Event Reporting Period**

Any AE occurrence during the study must be recorded on source documentation and eCRF at the site, in accordance with protocol instructions.

AEs and SAEs will be recorded from the first study drug administration through the Follow-up visit. After the Follow-up visit, only SAEs that are believed to be drug-related should be reported.

After informed consent, but prior to initiation of study drug, only SAEs considered by the investigator to be caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as blood collection). These procedure-related SAEs should only be reported on the source documents and SAE form, not on the AE eCRF. Subjects who undergo screening procedures but are not randomized into the study will not have SAEs recorded in the clinical database.

### **7.2.2 Eliciting Adverse Events**

Investigators will seek information on AEs and SAEs at each subject contact through the Follow-up visit. All AEs and SAEs, whether reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the AE eCRF page, and, if serious, on the SAE form. For each AE and SAE recorded, the investigator will make an assessment of seriousness, severity, and causality.

### 7.2.3 *Assessment of Severity*

All AEs entered into the eCRF will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 ([“Common Terminology Criteria for Adverse Events \(CTCAE\)” 2010](#)) to describe the maximum intensity of the adverse event.

If the AE cannot be found in the event-specific NCI CTCAE grading criteria, the investigator should use the definitions for Grade 1, 2, 3, and 4 in [Table 1](#).

**Table 1**                      **Adverse Event Grading**

Grade	Severity	Alternate Description <sup>a</sup>
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL <sup>b</sup> )
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL <sup>c</sup>
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE	

<sup>a</sup> Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing. A semi-colon indicates ‘or’ within the alternate description of the grade.

<sup>b</sup> Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>c</sup> Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 ([“Common Terminology Criteria for Adverse Events \(CTCAE\)” 2010](#))

Note that severity, a measure of intensity, is not equivalent to seriousness, a regulatory definition of outcome. Regardless of severity, some AEs may meet the criteria for seriousness. See [Section 7.1.2](#) for the definition of an SAE.

If an adverse event changes in severity during the same study period (e.g., treatment period), only the highest severity grade will be recorded on the eCRF.

### 7.2.4 *Assessment of Causality*

The investigator’s assessment of causality must be provided for all AEs (serious and non-serious). An investigator’s causality assessment is the determination of whether there exists a

reasonable possibility that the investigational product caused or contributed to an AE. Causality of an AE will be assessed by the investigator using the following terms:

- **Likely Related:** A reaction that follows a reasonable temporal sequence from administration of the study drug; that follows a known or expected response pattern to the suspected study drug; and for which other potential etiologies are considered less likely factors than the study drug.
- **Likely Unrelated:** A reaction that, considering all potential etiologies, is most likely due to factors other than the study drug.

### **7.3 Follow-up of Adverse Events and Serious Adverse Events**

The investigator must make every effort to follow all AEs and SAEs regardless of attribution until judged resolved or stabilized, the subject is lost to follow-up, or it has been determined that study drug treatment or participation in the study is not the cause of the AE or SAE.

### **7.4 Reporting Serious Adverse Events to the Sponsor and Institutional Review Board (IRB) or Ethics Committee (EC)**

The Sponsor or designee is under obligation to report certain SAEs to regulatory authorities related to investigational drugs in clinical trials. The Sponsor or designee must be notified within 24 hours of an AE when the investigator determines that an AE meets the protocol definition of an SAE, regardless of the cause or relationship to study drug.

An SAE related to study participation occurring before study drug administration and after informed consent should be promptly reported to the Sponsor. If the investigator learns of any SAE at any time after a participant has been discharged from the study, and the SAE is considered likely related to study drug, the SAE should be promptly reported to the Sponsor.

Please see the *MTI-109 SAE Report Form and Pregnancy Report Form Completion Guidelines* for safety reporting instructions.

The investigator must also comply with applicable requirements concerning reporting of SAEs to the Institutional Review Board (IRB) or Ethics Committee. This may include initial or follow-up notification of an SAE or other safety information.

### **7.5 Reporting Serious Adverse Events to Regulatory Authorities and Study Investigators**

The Sponsor, or its designee, is responsible for submitting reports of serious, unexpected related adverse events to regulatory authorities on an expedited basis, according to the ICH E2A Guideline and to other regulatory authorities according to national and local regulations as required. The Sponsor, or its designee, is responsible for prompt submission to the IRB or EC of any expedited SAE reports submitted to regulatory authorities. All investigators participating in ongoing clinical studies with serlopitant will receive copies of the SAE reports submitted on an expedited basis to regulatory authorities.

## 7.6 Emergency Unblinding

The investigator will immediately notify the Sponsor or the medical monitor to discuss the need for unblinding any subject via IWRS. There is no specific antidote for serlopitant and usual supportive medical management is recommended in the case of a medical emergency.

## 8 STATISTICAL METHODS

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. Endpoints will be summarized with descriptive statistics by treatment group and visit. For continuous variables, the following information will be presented: n, mean, standard deviation, median, minimum and maximum. For categorical variables counts and percentages will be used.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation. As one sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). As a second sensitivity analysis, a repeated measures model will be used on observed data.

Baseline for measures other than the eDiary and actigraphy daily measures, will be the last recorded value prior to the start of treatment. For daily measures including the WI-NRS, baseline will be the average result measured over the week prior to treatment. Additionally, the daily measures will be summarized at Weeks 2, 4, 6 and 8 by averaging the daily results associated with these weeks.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

### 8.1 Decision Rule and Sample Size

The decision rule is based on the Phase 2b screening methodology presented in Fleming and Richardson ([Fleming 2004](#)). The two-category decision guideline as applied to this clinical trial compares the observed one-sided p-value for the primary endpoint to two categories: (0.025, 0.05) and (0, 0.025).

- If the one-sided p-value is between 2.5% and 5% then the serlopitant-based regimen is plausibly efficacious and should be evaluated definitively in a subsequent Phase 3 clinical trial.
- If the one-sided p-value is less than 2.5%, then the serlopitant-based regimen will have met the generally accepted level of evidence required to demonstrate efficacy.

The sample size of 100 per group has been selected to achieve 90% power for the primary endpoint with



- 5% one-sided alpha and responder rates of 24% (placebo) and 43.5% (serlopitant)
- 2.5% one-sided alpha and responder rates of 24% (placebo) and 46% (serlopitant)

Testing of the key secondary endpoints will take place should statistical significance be reached for the primary endpoint. Testing within the key secondary endpoints will be hierarchical with testing starting with the WI-NRS Week 4 responder rate, then the Day 7 WI-NRS endpoint, and finally the Day 3 WI-NRS endpoint.

The sample size calculations have been performed in PASS 13 ([“PASS 13 Power Analysis and Sample Size Software” 2014](#)) and use a Chi-Squared test. The primary analysis will control for the stratification factors. It is expected that this unstratified power estimate will under-estimate the true power as it does not take the variance reduction resulting from stratification into account ([Matts 1988](#)).

## **8.2 Handling of Missing Data and Excluded Therapy Use**

Should a determination of treatment period (on treatment, pre-treatment) be required for adverse events or concomitant medication but the corresponding date is missing, or is a partial date, the event/medication will be considered on treatment unless the portions of the date that are available indicate this is not possible.

The primary method of handling missing efficacy data will be MCMC multiple imputation. Imputation will be conducted within each treatment group independently, so the pattern of missing observations in one treatment group cannot influence missing value estimations in another. For each imputation process, 25 imputations will be performed.

If a subject fails to complete their eDiary for a week or more the primary endpoint (WI-NRS), may be missing. If the Week 8 measure from the eDiary is unavailable because the subject withdrew from the study due to lack of efficacy, or the subject uses an excluded therapy to treat psoriasis or pruritus, their responder status will be defined as non-responder. If the Week 8 value is missing for any other reason, the WI-NRS change from baseline value will be based on imputed data. Missing Week 8 WI-NRS values from which the 4-point responder status is derived will be estimated by MCMC.

Missing WI-NRS data will be derived for the analysis using the method of MCMC multiple imputation. Since both primary and key secondary endpoints require WI-NRS, the following steps will be followed:

1. Using the daily eDiary data, calculate Baseline and Week 2 through Week 8 values by averaging available values. If any values are available, these will be used i.e. a minimum of 1 observation is required to compute a week's average.
2. From step 1, create a dataset for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing WI-NRS values in each dataset will be filled in using the MCMC method to generate 25 datasets.

The resulting datasets for each treatment arm will be combined into one complete dataset.

Syntax:

```
proc mi data=datain out=dataout seed=&seed. Nimpute=25 <options>;  
  where trtpn=(TRT); /* Note TRT = [1, 2]; depending on treatment group */;  
  mcmc chain=single;  
  var baseline d2 d3 d4 d5 d6 d7 week2 week3 week4 week5 week6 week7 week8;  
run;
```

3. From each complete dataset, the dichotomous responder rate will be determined.

Each complete dataset formed by multiply imputed data will be analyzed as specified for the particular analysis. The results from the analyses will be combined into a single inference using SAS® PROC MIANALYZE. In the case of the primary analysis and the secondary responder analyses, the Cochran Mantel Haenszel (CMH) statistics computed in the analyses of WI-NRS responder rates will be normalized using the Wilson-Hilferty transformation prior to combining them using SAS® PROC MIANALYZE

A total of 2 random seeds will be needed to impute missing data. Those random seeds have been pre-specified by using a random number generator:

- WI-NRS Serlopitant: Seed= 85162995
- WI-NRS Placebo: Seed= 878201528

### **8.3 Analysis Populations**

Primary efficacy analyses will be based upon an intent-to-treat (ITT) philosophy. The primary efficacy population will be the Full Analysis Set (FAS), which will include all randomized subjects who received at least one dose of study drug. Subjects will be analyzed within the treatment group to which they are randomized.

The primary safety population will be all treated subjects with at least one post-baseline assessment. For safety analyses, subjects will be classified based upon the treatment received.

Additional analyses performed on the Per Protocol (PP) population will be considered supportive. The PP population will include all subjects in the safety population who complete the Week 8 evaluations without any significant protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Received a strong CYP3A4 inhibitor (See [Appendix B](#));
- Received an excluded medication which may plausibly impact the primary endpoint at Week 8
- Have not been compliant with the dosing regimen (i.e. subjects must comply with 80–120% of the expected dosage of study medication during participation in the study);
- Have not completed Week 8 visit within  $\pm 7$  days window

Subjects who discontinue from the study drug due to an adverse event related to study treatment or documented lack of treatment effect, or who met protocol-defined non-responder criteria, will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the lists above to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

#### **8.4 Subject Disposition**

An accounting of all randomized subjects by disposition will be presented. Subjects who discontinue study drug prematurely or withdraw from the study will be summarized and listed, with a description of the reason for early termination/withdrawal.

#### **8.5 Subject Characteristics**

Demographic and other baseline characteristics will be summarized.

#### **8.6 Concomitant Medications**

Concomitant medications will be coded by the World Health Organization Drug Dictionary to Anatomical Therapeutic Classification (ATC) and preferred drug name. Concomitant medications will be summarized by ATC level and preferred drug name and listed.

#### **8.7 Treatment Compliance and Extent of Exposure**

Compliance with study drug dosing will be determined based on tablet counts recorded on the eCRF. Compliance will be calculated by analyzing expected number of tablets returned versus actual number of tablets returned. Summaries of treatment exposure will also be produced.

#### **8.8 Efficacy Analyses**

The efficacy endpoints will be summarized within the FAS and PP populations using descriptive statistics by time point and treatment. Results including averaged imputed values will be summarized at Baseline, Week 2, 4, 8 and Follow-up and the change from baseline for these measures will be summarized at Week 2, 4, 8 and Follow-up. The WI-NRS

measures will also be summarized at Week 6. The WI-NRS and change from baseline will also be presented for each study day. The PGIC is a measure of change and so will only be summarized at Week 2, 4, 8 and Follow-up.

For the 4 and 3 point responder rate endpoints, subjects will be considered responders if they have at least a 4 / 3 point reduction between baseline and the corresponding week and the subject did not use an excluded medication to treat their pruritus or psoriasis.

The difference in the primary efficacy outcome measure (WI-NRS 4-point responder rate at Week 8) will be tested using a CMH test controlling for the ‘as randomized’ stratification factors. Conceptually the hypotheses being tested are:

$$H_0: P_{Placebo} \geq P_{Serlopitant} \quad H_a: P_{Placebo} < P_{Serlopitant}$$

where  $P_{Placebo}$  is the percent of placebo responders and  $P_{Serlopitant}$  is the similar percent for serlopitant. The primary endpoint will utilize the missing data rules as outlined in [Section 8.2](#).

The remaining key secondary endpoints will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and stratification factor as fixed effects and the respective baseline values as a covariate. Both least squares means and observed means will be presented.

To confirm the assumptions for the ANCOVA model (i.e., that the errors are normally distributed with equal variances), residuals will be examined using the Shapiro-Wilk test. If there is overwhelmingly strong evidence that the assumptions are not satisfied, the data will be rank-transformed prior to submitting to the ANCOVA. Results of the rank-transformed analysis then will be considered the primary analysis; however, results of the non-rank-transformed analysis will also be presented.

The preceding analyses are to be conducted for the FAS and PP populations.

## **8.9 Sensitivity Analyses**

### **8.9.1 Last Observation Carried Forward**

As a sensitivity analysis, missing values will be imputed using LOCF. Each primary and key secondary endpoint will be analyzed as it was using the multiply imputed data.

## **8.10 Psychometric Analyses**

A psychometric assessment of the WI-NRS will be conducted to assess test-retest reliability, construct validity and responsiveness. These will be conducted outside of the statistical analysis plan for this study and will include analyses of: intra-class correlation coefficients (ICC), Pearson’s correlations, and change scores for test-retest reliability; Pearson Product Moment or Spearman Correlations for concurrent validity; t-test analyses or ANOVA for known groups validity; and correlations of change scores for WI-NRS and other measures for

responsiveness. Anchor- and distribution-based methods also will be used to assess responsiveness as well as support a responder definition.

## **8.11 Safety Analyses**

### **8.11.1 Adverse Events**

The incidence of all AEs and treatment-related AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. An overview of AEs, which includes subject incidence of AEs, treatment-related AEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

SAEs will be listed and summarized in a similar manner to AEs.

### **8.11.2 Clinical Safety Laboratory Results**

Clinical safety laboratory values will be measured by a central laboratory. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Graphs of laboratory values over time will also be produced.

Subjects with clinical laboratory values outside of the normal reference range at any post-baseline assessment will be summarized. Shifts from baseline laboratory values will be tabulated.

### **8.11.3 Vital Signs**

The observed data and change from baseline for each measurement day will be summarized with descriptive statistics.

### **8.11.4 Electrocardiograms**

The overall ECG assessment (abnormal or normal) will be summarized along with a summary of how many subjects developed a post treatment abnormal result. The study relevance of the finding (i.e. clinical significance as determined by the investigator) will be provided in a listing.

### **8.11.5 Physical Exams**

Physical exam finds will be recorded by the sites within medical history or adverse events and otherwise not summarized.

## **8.12 Pharmacokinetics Analysis**

The plasma concentrations of serlopitant and metabolites will be reported in a PK report that will be a part of the clinical study report.

The plasma concentrations of serlopitant and metabolites will also be combined with the data from other serlopitant clinical studies for population PK analysis with PK endpoint of individual model parameter estimates and covariates identification. A specific population PK data analysis plan will be developed that will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques. The population PK analysis report will not be a part of the clinical study report.

## **9 ADMINISTRATIVE ASPECTS**

### **9.1 Changes to the Protocol**

Protocol amendments must be made only with the prior written approval of the Sponsor. An investigator signature will be obtained for the initial protocol and any amendments. Substantial amendments will be provided to the appropriate regulatory authorities. No protocol changes affecting the following will be made without the written approval of the Sponsor and the responsible IRB:

- Safety and/or eligibility of subjects
- Data integrity
- Study design or conduct
- Willingness of a subject to participate in the study

### **9.2 Study Termination**

The Sponsor has the right to terminate this study at any time. Reasons may include, but are not limited to, evidence of a potential safety risk in this study or other serlopitant studies or poor enrollment. A written statement fully documenting the reasons for study termination will be provided to the IRB.

### **9.3 Monitoring and Auditing Procedures**

The Sponsor will designate study monitors who will be responsible for monitoring the conduct of this study. A separate study Monitoring Plan will include details regarding the responsibilities of the study monitors, investigator responsibilities in providing access to records and addressing issues identified, the frequency and structure of monitoring visits, and adherence to subject confidentiality as outlined in the Informed Consent Form (ICF).

### **9.4 Transfer of Obligations**

The Sponsor will delegate certain aspects of study oversight to Contract Research Organizations (CROs). The specific responsibilities will be detailed in Transfer of Obligations documents.

## **9.5 Informed Consent**

The purpose of the study, the procedures to be carried out, and any potential risks of study participation will be described in non-technical terms in the ICF. After having reviewed and understood the ICF, subjects will be required to read, sign, and date an IRB-approved consent form before any study-specific procedures are carried out. Subjects will be assured that they may withdraw from the study at any time without jeopardizing medical care related to or required as a result of study participation. The original signed consent form will be maintained in the investigator site file. Copies of signed consent forms will be provided to the subject.

## **9.6 Communication with the Institutional Review Board**

The IRB is constituted and operates in accordance with the principles and requirements described in the ICH E6 guideline. The protocol, informed consent form, other written subject information, and any proposed study advertising material must be submitted to the IRB for written approval. IRB approval of these documents will be provided to the investigator. The study will not start until the IRB has granted its approval of the study materials and procedures.

Protocol amendments will be submitted to the IRB as explained in [Section 9.1](#). SAE information will be submitted to the IRB as explained in [Section 7.4](#).

If the study is terminated by the Sponsor, a written statement fully documenting the reason(s) for study termination will be provided to the IRB.

## **9.7 Disclosure and Confidentiality**

By signing this protocol, the investigator agrees to keep all information provided by the Sponsor in strict confidence and to require the same confidentiality from site staff and the IRB. Study documents provided by the Sponsor (e.g., protocol, IB, eCRFs) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

The investigator must ensure that the subjects be identified by a unique subject study number. Other study-related documents that may contain confidential participant information (e.g., signed ICFs) will be kept in strict confidence by the investigator and be stored in a secure location with access restricted to the study staff.

## **9.8 Records and Electronic Case Report Forms**

All study data except central laboratory, PK, eDiary, actigraphy, and ECG data will be recorded in an eCRF system. Data will be entered at the site by the appropriately designated and trained site personnel. All source documents from which eCRF entries are derived should be placed in the subject's medical records. eCRFs will be completed for every subject screened in the study.

The study monitor will review all eCRFs in detail and will have access to participant medical records, laboratory data, and other source documentation to allow required eCRF fields to be verified by source data.

Data consistency and plausibility checks against data entered into the eCRF will be included in the eCRF system. Data corrections can be performed in the eCRFs by the site. For each instance of data modification, the system requires a reason for change. The system keeps a full audit trail of the data values, the date and time of modification, and the electronic signature of the user who performed the change.

After a full review of the eCRFs by the study monitor and resolution of any data clarifications, the investigator will review, sign, and approve the subject's eCRF. All essential documents, source data, clinical records, and laboratory data will be retained by the site in accordance with the ICH E6 guideline and the site's data retention policies. These records must be available for inspection by the Sponsor, monitor, and regulatory authorities.

Further detail regarding data management and eCRFs is included in the Data Management Plan.

## **9.9 Good Clinical Practices and Ethical Study Conduct**

The study procedures outlined in this protocol will be conducted in accordance with applicable ICH Guidelines, including ICH E6: Good Clinical Practices. As this study is conducted under a US IND, the investigator will also ensure that the basic principles of "Good Clinical Practice", as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators", 21 CFR, part 50 and 21 CFR, part 56 are adhered to.

The study procedures outlined in this protocol will also be conducted in accordance with the principles of the Declaration of Helsinki.

## **9.10 End of Study Notification**

The Sponsor will notify appropriate regulatory authorities and the IRB within 90 days from the end of the clinical study. The end of the clinical study is defined as the last study visit for the last subject.

## **9.11 Publication of Results**

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study or relying on data from this study must be submitted to the Sponsor for review and release before submission for publication. The Sponsor is responsible for final approval of all publications.

## **9.12 Final Report**

A clinical trial summary report will be provided to the appropriate regulatory authorities within one year of the end of the clinical study.



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## APPENDIX A SCHEDULE OF ACTIVITIES AND ASSESSMENTS

**Table 2 Schedule of Visit Activities**

Examination	Screening <sup>1</sup>	Mid-Screening <sup>2</sup>	Base-line <sup>3</sup>	Week 1 <sup>2</sup>	Week 2	Week 4	Week 6 <sup>2</sup>	Week 8	F/U <sup>4</sup>	Comments
<b>Visit Window in Days (d)</b>			+3 d	±3 d	±2 d	±3 d	±3 d	±3 d	+3 d <sup>4</sup>	All visits and window should be scheduled based on the Baseline visit (Day 1)
Informed consent	X									
Demographics	X									
Medical history (including prior medications)	X									
I/E criteria	X		X							
Randomization			X							
Physical exam	X				X	X		X	X	Screening physical exam is complete; other exams are targeted.
Vital signs	X		X		X	X		X	X	Heart rate, sitting blood pressure, respiration rate, and temperature. Height will be assessed at screening; Weight will be assessed at all scheduled clinic visits.
ECG	X					X			X	
Labs	X		X*			X		X	X	Screening labs (hematology, chemistry, and urinalysis), including urine pregnancy test, may be collected during the screening period (after Screening visit but prior to the Baseline visit); endocrine and reproductive endocrine labs will be collected at screening, Week 8, and F/U. *At the Baseline visit, only a urine pregnancy test for females of childbearing potential will be collected. Serum pregnancy tests will be collected to confirm any positive urine test results.
PK						X		X		
BSA	X		X		X	X		X	X	
PGA			X		X	X		X	X	
sPGA	X		X		X	X		X	X	
PGIC					X	X		X	X	
PIQ			X			X		X	X	
Dispense/collect eDiary and actigraphy watches	X		X		X	X		X	X	Actigraphy watches replaced at every visit. eDiary and actigraphy watches will be dispensed at the Screening visit and returned at the Follow-up visit.
eDiary review		X	X	X	X	X	X	X	X	See <a href="#">Table 3</a> for eDiary assessments.
IP dispensation			X		X	X				
IP accountability/return					X	X		X	X**	**For subjects who discontinue study drug early between visits.
Concomitant medications		X	X	X	X	X	X	X	X	
AEs		X	X	X	X	X	X	X	X	During the period between informed consent and first study drug dose, only SAEs caused by a protocol-mandated intervention will be collected.

<sup>1</sup> Subjects requiring a washout will perform the Screening visit 4 weeks prior to the Baseline visit. Subjects not requiring a washout will perform the Screening visit 2 weeks prior to the Baseline visit.

<sup>2</sup> Telephone Contact. The Mid-Screening telephone contact should only occur for subjects who require a washout of medication, at least 15 days prior to the scheduled Baseline visit.

<sup>3</sup> Baseline Assessments must be done prior to randomization and initial study drug administration.

<sup>4</sup> The Follow-up (F/U) visit occurs 14 days (+ 3 days) after the Week 8 visit or the last dose of study drug for subjects who discontinue study drug early.

**Table 3                      Schedule of eDiary and Actigraphy Assessments**

eDiary and actigraphy devices are provided to subjects at the Screening visit. eDiary and actigraphy devices are collected at the Follow-up Visit.

<b>Device</b>	<b>Assessment</b>	<b>Frequency and Duration of Assessment</b>	<b>Comments</b>
eDiary	WI-NRS	Once daily from Screening visit through the Follow-up visit.	
eDiary	Dosing	Once daily from Baseline visit through Week 8 visit or study drug discontinuation.	
Actigraphy watch	Scratching	Continuous nighttime monitoring from Screening visit through the Follow-up visit.	Download data and replace watches at each study visit.
Actigraphy watch	Sleep	Continuous nighttime monitoring from Screening visit through the Follow-up visit.	Download data and replace watches at each study visit.

## APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

The list of strong CYP3A4 inhibitors is based on the FDA list effective September 26, 2016, *Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling)* (“Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)”):

1. boceprevir
2. clarithromycin
3. cobicistat
4. conivaptan
5. danoprevir and ritonavir
6. diltiazem
7. elvitegravir and ritonavir
8. regular grapefruit juice consumption
9. idelalisib
10. indinavir and ritonavir
11. itraconazole<sup>a</sup>
12. ketoconazole<sup>a</sup>
13. lopinavir and ritonavir
14. nefazodone
15. nelfinavir
16. paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
17. posaconazole<sup>a</sup>
18. ritonavir
19. saquinavir and ritonavir
20. telaprevir
21. tipranavir and ritonavir
22. troleandomycin
23. voriconazole<sup>a</sup>

<sup>a</sup> Topical formulations of azoles are not considered strong CYP3A4 inhibitors due to limited systemic absorption.

**APPENDIX C      PATIENT-REPORTED OUTCOMES MEASUREMENT  
INFORMATION SYSTEM ITCH QUESTIONNAIRE**

## Itch – General – Short Form 8a

Please respond to each question or statement by marking one box per row.

**In the past 7 days...**

		Never	Rarely	Sometimes	Often	Almost always
PIQGeneral64	Because of itch, I was absent from work.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral65	Because of itch, it was hard to work.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral56	Because of itch, it was hard to do even simple tasks.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral54	Because of itch, I made more mistakes than normal.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral49	Because of itch, it was hard to watch television.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral48	Because of itch, it was hard to shower or take a bath.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral67	Because of itch, I avoided being around people.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQGeneral77	Because of itch, it was hard to interact with my family.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5



**Itch – Scratching Behavior 5a****Please respond to each question or statement by marking one box per row.****In the past 7 days...**

		<b>Never</b>	<b>Rarely</b>	<b>Sometimes</b>	<b>Often</b>	<b>Almost always</b>
PIQScratch81	I scratched myself until I bled.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQScratch84	It was hard to stop scratching or rubbing.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

		<b>Not at all</b>	<b>A little bit</b>	<b>Somewhat</b>	<b>Quite a bit</b>	<b>Very Much</b>
PIQScratch85	I worried about having open wounds from scratching.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQScratch82	I worried about flaking skin from scratching.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQScratch83	I worried about getting scars from scratching.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

## Itch – Mood and Sleep – Short Form 8a

Please respond to each question or statement by marking one box per row.

**In the past 7 days...**

		<b>Never</b>	<b>Rarely</b>	<b>Sometimes</b>	<b>Often</b>	<b>Almost always</b>
PIQMoodSleep40	Because of itch, I felt miserable.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep42	Because of itch, I felt embarrassed.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep37	Because of itch, I felt sad.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep32	Because of itch, I was nervous.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep58	Because of itch, I was restless.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep60	Because of itch, I had difficulty falling asleep.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep61	Because of itch, I had trouble staying asleep.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQMoodSleep63	Because of itch, my sleep was restless.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

## Itch – Activity and Clothing– Short Form 8a

Please respond to each question or statement by marking one box per row.

**In the past 7 days...**

		Never	Rarely	Sometimes	Often	Almost always
PIQActivCloth31	Because of itch, my physical activities were limited.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth20	Because of itch, it was hard to do activities that made me sweat.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth18	Because of itch, it was hard to do light physical activity.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth17	Because of itch, it was hard to do moderate physical activity, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth16	Because of itch, it was hard to do vigorous physical activity, such as running, lifting heavy objects, or participating in strenuous sports.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth19	Because of itch, I sat around more than usual.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth23	Because of itch, I limited the clothing I could wear.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PIQActivCloth24	Because of itch, it was hard to wear short-sleeves.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5