

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 AND ADOLESCENTS WITH A HISTORY OF ATOPIC DERMATITIS (ATOMIK)

IND No.: 117780

ClinicalTrials.gov ID: NCT02975206

Protocol No.: MTI-103

Protocol Version / Date: Version 3.0 / 21-NOV-2017

Development Phase: Phase 2

Sponsor: Menlo Therapeutics Inc.
200 Cardinal Way, 2nd Floor
Redwood City, CA 94063
USA

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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.

Principal Investigator's printed name

Principal Investigator's signature

Date (DD-MMM-YYYY)

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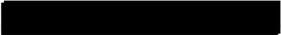
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Approved by:


Senior Vice President,
Clinical Development


Signature

21-NOV-2017
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 and Adolescents with a History of Atopic Dermatitis (ATOMIK)
Protocol Number:	MTI-103
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 and adolescents with a history of atopic dermatitis.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> • To assess the safety and tolerability of repeated oral doses of serlopitant in adults and adolescents with a history of atopic dermatitis. • To assess the psychometric properties of Worst-Itch Numeric Rating Scale (WI-NRS).
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 and adolescents with a history of atopic dermatitis. Subjects who meet the study entry criteria will be randomized in a 1:1:1 ratio to receive daily oral doses of serlopitant 1 mg, 5 mg, or placebo for 6 weeks. The study will be conducted at approximately 40 study sites.</p> <p>The study will consist of three periods, for a total study period of approximately 12 weeks:</p> <ul style="list-style-type: none"> • Screening period: 2 weeks • Treatment period: 6 weeks • Follow-up period: 4 weeks <p>During the screening period, subjects will undergo eligibility evaluation and will have their baseline symptom scores established. 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 1 mg, serlopitant 5 mg, or placebo. Subjects will take a loading dose (3 tablets taken orally) at bedtime on the first day of the treatment period (Study Day 1). Starting on Study Day 2, subjects will take one tablet per day taken orally at bedtime. Subjects will be instructed to take all doses at approximately the same time each day and no sooner than 2 hours before or after a meal.</p> <p>The primary efficacy endpoint will be assessed during Week 6 of treatment.</p> <p>After completion of the 6-week treatment period, all subjects will enter a 4-week follow-up period. Subjects who discontinue treatment early at any time during the treatment period will have an Early Treatment Discontinuation (ETD) visit within 7 days after their last dose of study drug in addition to a follow-up visit.</p>

<p>Safety Review:</p>	<p>An independent Data Monitoring Committee (iDMC) will be established to monitor unblinded safety data on a regular basis throughout the study. The iDMC may make recommendations to the Sponsor to continue or terminate the study based upon the outcomes of the data reviews.</p> <p>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.</p>
<p>Planned Sample Size:</p>	<p>Approximately 450 subjects will be randomized.</p>
<p>Study Population:</p>	<p>The study will consist of adults and adolescents with a history of atopic dermatitis who have pruritus despite treatment with standard of care anti-pruritic therapies.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male or female, age 13 years or older at consent/assent. <ol style="list-style-type: none"> a. For subjects below the legal age of consent, the subject must be willing and able to provide assent and to comply with study visits and study-related requirements and his/her parent(s)/guardian(s) must be willing and able to provide written informed consent. 2. Pruritus of at least 4 weeks duration prior to the initial Screening visit and during the 2-week screening period, despite treatment with standard of care anti-pruritic therapies such as H1 antihistamines or emollients. <ol style="list-style-type: none"> a. Subjects using stable doses of oral H1 antihistamines at the initial Screening visit must be willing to continue these at the same doses and frequencies throughout the study inclusive of the follow-up period. 3. WI-NRS score ≥ 7 in the 24-hour period prior to the initial Screening visit. 4. Average weekly WI-NRS score ≥ 6 for each week of the Screening period, as recorded in the eDiary. 5. Diagnosis of atopic dermatitis, as defined by the 2014 American Academy of Dermatology (AAD) Guidelines of Care for the Management of Atopic Dermatitis.¹ <ol style="list-style-type: none"> a. Subjects with active atopic dermatitis skin involvement must have had stable skin disease, defined as experiencing no disease flares, for at least 4 weeks immediately prior to randomization. Subjects using stable doses of bland emollients, topical calcineurin inhibitors, and/or low- to mid-potency topical corticosteroids at the initial Screening visit must be willing to continue these at the same doses and frequencies throughout the study. b. Subjects without active atopic dermatitis skin involvement must have had a past diagnosis of atopic dermatitis, supported by written records documenting the presence of features consistent with the 2014 AAD Guidelines. 6. All female subjects who are of childbearing potential must 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 4 weeks after last dose of study drug. All fertile male subjects, with partners who are females of childbearing potential, must use condoms from randomization until 4 weeks after last dose of study

	<p>drug. All subjects who are fertile males or females of childbearing potential must also refrain from sperm/egg donation starting from first dose of study drug and until 4 weeks after last dose of study drug. Please refer to Section 7.1.5 for acceptable methods of contraception.</p> <ol style="list-style-type: none">7. Weight \geq 32 kg at the baseline visit.8. Willing and able to complete once-daily eDiary entries within a consistent timeframe for the duration of the study.<ol style="list-style-type: none">a. Subjects must have \geq 80% eDiary completion rate during the screening period.9. Judged to be in good health in the investigator's opinion. <p>Exclusion Criteria:</p> <ol style="list-style-type: none">1. Prior treatment with serlopitant or other neurokinin-1 receptor (NK₁-R) antagonists (e.g. aprepitant).2. Clearly defined etiology for pruritus other than atopic dermatitis. These include but are not limited to urticaria, psoriasis or other non-atopic dermatologic conditions, hepatic or renal disease, psychogenic pruritus, drug reaction, untreated hyperthyroidism, and infection.3. Presence of any acute condition which may risk inducing an atopic dermatitis flare during the course of the study, such as impetigo or active herpes simplex infection.4. Treatment with systemic corticosteroids within 4 weeks prior to randomization.<ol style="list-style-type: none">a. Treatment with non-systemic corticosteroids that do not involve skin application (e.g. inhaled, intranasal, or intra-articular corticosteroids) will be permitted.5. Treatment with Class III or higher potency topical corticosteroids² or any topical anti-pruritic therapies (other than stable doses low- or mid-potency topical corticosteroids, topical calcineurin inhibitors, or bland emollients) within 2 weeks prior to randomization.6. Treatment with systemic therapies with recognized anti-pruritic (e.g. tricyclic antidepressants, sedatives, tranquilizers, gabapentin, marijuana or other cannabinoids, opioid receptor agonists/antagonists) or pruritic (e.g. opioids, angiotensin-converting enzyme inhibitors, cocaine, antimalarials) properties within 4 weeks prior to randomization.<ol style="list-style-type: none">a. Stable doses of H1 antihistamines will be permitted (see Inclusion Criterion 2a).7. For subjects using bland emollients, low- or mid-potency topical corticosteroids, topical calcineurin inhibitors, and/or oral H1 antihistamines, any clinically significant changes in dose or frequency during the screening period.8. Treatment with systemic immunosuppressive/ immunomodulatory therapies within 4 weeks prior to randomization (including but not limited to phosphodiesterase-4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, interferon-gamma, or phototherapy).9. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer.10. Treatment with strong CYP3A4 inhibitors within 4 weeks prior to randomization (see Appendix B).
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	<ol style="list-style-type: none"> 11. Use of an indoor tanning facility within 4 weeks prior to randomization. 12. Treatment with any investigational therapy within 4 weeks prior to randomization. 13. Allergen immunotherapy within 6 months prior to randomization. 14. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x the upper limit of normal (ULN) during screening. 15. 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. 16. History of a major psychiatric condition (including major depressive disorder, bipolar disorder, or schizophrenia), suicidal ideation, or suicide attempt. 17. Known active hepatitis infection. 18. Known history of human immunodeficiency virus (HIV) infection. 19. Documented history of parasitic infection, including skin parasites such as scabies, within 12 months prior to randomization. 20. Known active parasitic infection. 21. Regular long-distance running (e.g. 10Ks, marathons) or long-distance bicycling (e.g. 30 + miles) and/or strenuous physical activity (e.g. bodybuilding) within 2 weeks prior to randomization. 22. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject, including clinically significant ECG abnormalities during screening. 23. History of hypersensitivity to serlopitant or any of its components. 24. Currently pregnant or breastfeeding, or male subject with a pregnant or breastfeeding partner. 25. Females of childbearing potential who are unable or unwilling to practice highly effective contraception (pregnancy prevention); fertile males who are unable or unwilling to use condoms with female partners of childbearing potential.
Study Drug:	Serlopitant 1 mg and 5 mg oral tablets and matching placebo.
Dosage:	<p>Serlopitant: 1 mg or 5 mg once daily by mouth for 6 weeks, following a 3-tablet loading dose on the first day of the treatment period.</p> <p>Matching placebo: Once daily by mouth for 6 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 change in WI-NRS from baseline to Week 6.
Secondary Efficacy Endpoints:	<p>The key secondary efficacy endpoints are as follows:</p> <ul style="list-style-type: none"> • WI-NRS 4-point responder rate at Week 6 • Change in ItchyQoL from baseline to Week 6 <p>Additional secondary efficacy endpoints include the following:</p> <ul style="list-style-type: none"> • WI-NRS 3-point responder rates • Change in Average-Itch NRS (AI-NRS) and AI-NRS responder rates • Change in 5-D Pruritus Scale

	<ul style="list-style-type: none"> • Change in Static Patient Global Assessment of Itch Severity (sPGA) • Change in Patient Global Impression of Change in Itch Severity (PGIC) • Change in number of night-time scratching events per hour from baseline to Week 6
Safety Endpoints:	<p>Safety endpoints include the following:</p> <ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Change in clinical laboratory parameters following study drug exposure • Changes in vital sign and electrocardiogram (ECG) parameters following study drug exposure • Plasma concentrations of serlopitant and metabolites
Exploratory Endpoints:	<p>Exploratory endpoints include the following:</p> <ul style="list-style-type: none"> • Change in Investigators' Global Assessment of atopic dermatitis severity (IGA-AD) • Change in sleep efficiency • Change in mean activity during the sleep period
Decision Rule and Sample Size	<p>A stepdown procedure will be used to control for multiplicity of dose groups with testing starting with the 5 mg group and then proceeding to the 1 mg group. A gatekeeper procedure within dosing group will be used for the key secondary endpoints.</p> <p>The sample size of 150 per group has been selected to achieve 90% power for the pairwise tests with a 5% one-sided alpha level assuming a treatment effect (placebo change from baseline - serlopitant change from baseline) of -1 and a standard deviation of 2.9.</p>
Statistical Methods:	<p>Efficacy analyses will be based upon an intent-to-treat philosophy. The primary efficacy population will be the Full Analysis Set (FAS) that will include all randomized and treated subjects. Subjects will be analyzed within the treatment group to which they are randomized.</p> <p>Efficacy Analyses:</p> <p>The primary efficacy endpoint will be tested using an analysis of variance (ANOVA) model controlling for the stratification factors. A main effects model with an interaction term (treatment by stratification factors) and a Type II hypothesis will be used. Missing data imputation will be used for subjects who fail to complete the eDiary at Week 6 or receive excluded therapy. The primary endpoint will be summarized with descriptive statistics by treatment group and study week. These summary statistics will include estimates of the treatment differences and associated confidence interval.</p> <p>Testing, using an analysis of variance (ANOVA) model or Cochran Mantel Haenszel (CMH) test of the key secondary endpoints will also 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</p>

	<p>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
Planned Dates of Study:	Oct 2016-Dec 2017
Expected Duration of Subject's Participation	Approximately 12 weeks: 2 weeks of screening, 6 weeks of treatment, and a follow-up period of 4 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAD	American Academy of Dermatology
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
AI-NRS	Average-Itch Numeric Rating Scale
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BOCF	Baseline Observation Carried Forward
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ETD	Early treatment discontinuation
FAS	Full Analysis Set
iDMC	Independent Data Monitoring Committee
ICF	Informed Consent Form
IGA-AD	Investigators' Global Assessment of atopic dermatitis severity
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK ₁ -R	Neurokinin-1 receptor
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
QoL	Quality of life
SAE	Serious adverse event
SOC	System organ class
SP	Substance P
sPGA	Static Patient Global Assessment
TEAE	Treatment-emergent adverse event
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Atopic Dermatitis and Pruritus

Atopic dermatitis (AD, atopic eczema, eczema) is an inflammatory, chronically relapsing and intensely pruritic skin disease occurring often in families with atopic diseases (AD, asthma, and/or allergic rhinoconjunctivitis).³ It is frequently referred to as “the itch that rashes,”⁴ highlighting the central role that pruritus plays in AD pathology. Pruritus is the “cardinal symptom” in AD⁵ and it has been characterized as the “most distressing” symptom of AD.⁶ Mollanazar et al⁷ describe a prevalence of 58%-91% of chronic pruritus in patients with AD. Overall, pruritus is responsible for much of the disease burden borne by patients and their families.¹

1.2 Substance P and the Neurokinin-1 Receptor

The itch/scratch cycle is a hallmark of atopic dermatitis and is a major factor in perpetuating the disease.⁶ The itch in atopic dermatitis often begins without visible lesions^{8,9} and has been shown to involve altered sensory responses to exogenous and endogenous stimuli^{10,11} as well as modifications in sensory innervation of involved skin, including increased density of substance P-positive nerve fibers.¹²

Substance P (SP) is an undecapeptide that belongs to the tachykinin family of neuropeptides, a group that also includes neurokinin A and neurokinin B.¹³ SP has been implicated in a number of biological functions, both physiological and pathophysiological, including pruritus perception, vomiting reflex, pain perception, and immunomodulatory responses.^{14,15,16} The role of SP in pruritic conditions has been supported by evidence of increased serum levels in atopic dermatitis,¹⁷ as well as other pruritic diseases such as cholestatic pruritus,¹⁸ and prurigo nodularis.¹⁹

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, neurokinin-2, and neurokinin-3 receptors.²⁰ The neurokinin-1 receptor (NK₁-R) in particular has been studied in great detail. NK₁-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.

NK₁-R stimulation has been shown to be an important pathway for pruritus perception.²¹ Inhibition of this pathway results in decreased pruritus and scratching reflexes in animal models.²² More importantly, a commercially available NK₁-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^{23,24,25} and erlotinib-induced pruritus.^{26,27} 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.²⁸

1.3 Serlopitant

1.3.1 Serlopitant Background

Serlopitant is a small molecule, highly selective NK₁-R antagonist that is administered orally and metabolized by CYP3A4, with a plasma half-life of 70-80 hours. It binds with high affinity to the human NK₁-R with a dissociation constant (K_d) of 46 pM; displacing SP binding with a half-maximal inhibition concentration (IC₅₀) 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 humans, serlopitant has been evaluated in over 850 subjects across thirteen Phase 1 studies and three completed Phase 2 studies. Escalating single doses up to 400 mg have been well tolerated in healthy young males. Multiple doses of up to 50 mg a day for 4 weeks have been well tolerated in healthy young 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. Forty-one (41) subjects received 4 mg liquid filled capsule (LFC) daily (bioequivalent to 5 mg tablets) for 1 year. Plasma concentrations of serlopitant appear to increase in a dose-proportional fashion in both young males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young and elderly subjects.

In the Phase 1 studies, no drug-related serious adverse events (SAEs) were observed. The most commonly reported adverse events (AEs) in subjects who received serlopitant in the Phase 1 studies were headache (15%), diarrhea (5%), dizziness (5%), drowsiness (4%), nausea (4%), somnolence (3%), abdominal discomfort (3%), loose stools (3%), cough (3%), cold (3%) sore throat (3%) and tiredness (2%). Laboratory abnormalities noted were transient microscopic hematuria (4%) and mild transient elevation of liver function tests (2 to < 3 fold increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (2%).

In a Phase 2 study examining treatment of overactive bladder (Study P003), the most common clinical AEs 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%).

1.3.2 Serlopitant in Chronic Pruritus

Serlopitant has been evaluated in a Phase 2 study of subjects with chronic pruritus (TCP-101). A Phase 2 study in subjects with prurigo nodularis (TCP-102) has been conducted in Germany; the clinical study report is under preparation.

TCP-101

Study design: a total of 257 adult subjects 18-65 years of age with chronic pruritus were randomized to receive one of 4 dose groups: placebo (64 subjects), serlopitant 0.25 mg

(64 subjects), serlopitant 1 mg (65 subjects), and serlopitant 5 mg (64 subjects). 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 visual analog scale (VAS), summarized as a percentage change from baseline.

Efficacy results: The mean percent decreases from baseline VAS scores were larger in the active-treatment groups versus placebo at every scheduled post-baseline study visit. The largest pairwise differences of least squares means versus placebo occurred in the serlopitant 1 mg group (p-value < 0.05 at study Weeks 1, 3, 4, 5, 6, and 10). Similar results were seen in the serlopitant 5 mg group for the least squares mean differences versus placebo (p-value < 0.05 at study Weeks 3, 4, 5, 6, and 10).

Safety results: Treatment-emergent adverse events (TEAEs) were reported in 25.4% of subjects in the placebo group and in 31.3%, 36.9%, and 37.5% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. "Infections and Infestations" was the system organ class (SOC) with the highest incidence of TEAEs.

Overall, headache was the most commonly-reported TEAE, reported in 6.3% of subjects in the placebo group and in 1.6%, 4.6%, and 1.6% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. Somnolence and diarrhea were the TEAEs with the highest overall incidence in the active-treatment groups. Somnolence was reported in 1.6% of subjects in the placebo group and in 1.6%, 4.6%, and 4.7% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. Diarrhea occurred in 1.6% of subjects in the placebo group and in 0%, 6.2%, and 3.1% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively.

Most of the TEAEs were mild or moderate in severity. Two severe TEAEs were reported: hypothyroidism in 1 subject in the serlopitant 0.25 mg group and peripheral neuropathy in 1 subject in the serlopitant 5 mg group. Both of these events were considered not related to study treatment.

Treatment-related TEAEs were reported in 7.9% of subjects in the placebo group and in 10.9%, 13.8%, and 12.5% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. "Nervous systems disorders" was the SOC with the highest incidence of treatment-related events.

One SAE (spontaneous abortion) occurred in a subject in the serlopitant group. This event was considered not related to study treatment. Six subjects (3 in the placebo group, 1 in the serlopitant 1 mg group, and 2 in the serlopitant 5 mg group) discontinued the study as a result of a TEAE. Two of these subjects had events considered not related to study treatment (pruritus in 2 subjects) and 3 subjects had events considered to be treatment related (headache in 1 subject; diarrhea in 1 subject; and symptoms of a panic attack in 1 subject).

There was no evidence of meaningful trends in laboratory abnormalities or changes in vital signs. Two subjects had a clinically significant change in an electrocardiogram (ECG). One subject in the serlopitant 0.25 mg group had a normal ECG at screening and Visit 4 but at Visit 6 was noted to have supraventricular extrasystoles and ectopic atrial rhythm. These

changes were considered mild and possibly due to study drug but required no treatment. One subject in the serlopitant 5 mg group had first degree AV block at screening, Visit 4 and Visit 6. Although the ECG interpretation was the same at each time point, the investigator considered the on-study findings clinically significant. No treatment was required.

These results, together with the extensive safety experience with serlopitant to date, the scientific rationale for neurokinin-1 receptor (NK₁-R) inhibition in the treatment of pruritus, and the previously published human data with aprepitant, serve to support the evaluation of serlopitant for the treatment of pruritus in patients with atopic dermatitis.

2 STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of serlopitant for the treatment of pruritus in adults and adolescents with a history of atopic dermatitis.

The secondary objectives of this study are as follows:

- To assess the safety and tolerability of repeated oral doses of serlopitant in adults and adolescents with a history of atopic dermatitis
- To assess the psychometric properties of the 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 and adolescents with a history of atopic dermatitis. Approximately 450 subjects who meet the study entry criteria will be randomized in a 1:1:1 ratio to receive daily oral doses of serlopitant 1 mg, 5 mg, or placebo for 6 weeks. The study will be conducted at approximately 40 study sites.

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

- Screening period: 2 weeks
- Treatment period: 6 weeks
- Follow-up period: 4 weeks

Informed consent will occur prior to any protocol-mandated procedures, including the stopping of any excluded therapies. This may occur prior to the initial Screening visit. During the screening period, subjects will undergo eligibility evaluation and will have their baseline symptom scores established. 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 therapies for the duration of the study. Subjects who meet initial screening requirements will be provided with an electronic device for recording eDiary assessments throughout the study.

At the baseline visit, eligible subjects will be randomly assigned to receive study drug (serlopitant 1 mg, serlopitant 5 mg, or placebo). Subjects will take a loading dose (3 tablets taken orally) at bedtime on the first day of the treatment period (Study Day 1). Starting on Study Day 2, subjects will take one tablet per day taken orally at bedtime. Subjects will be instructed to take all doses at approximately the same time each day and no sooner than 2 hours before or after a meal. The primary efficacy endpoint will be assessed during Week 6 of treatment.

After completion of the 6-week treatment period, all subjects will enter a 4-week follow-up period. Subjects who discontinue treatment early at any time during the treatment period will have an Early Treatment Discontinuation (ETD) visit within 7 days after their last dose of study drug in addition to a follow-up visit.

3.2 Rationale for Study Design and Dose Selection

In the TCP-101 study, serlopitant demonstrated superior efficacy compared to placebo for the treatment of chronic pruritus in a broad population of subjects (N = 257), including subjects with atopic diathesis (i.e. history of atopic dermatitis, asthma, and/or allergic rhinitis). The superior efficacy was observed at multiple timepoints with both the serlopitant 1 mg and 5 mg doses, but not with the serlopitant 0.25 mg dose. Safety profiles between the three serlopitant doses were comparable, and serlopitant was generally well-tolerated at the doses evaluated.

The current MTI-103 study is designed to confirm the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus, specifically in patients with a history of atopic dermatitis. Although the TCP-101 study included subjects with a history of atopic dermatitis, the greater number of subjects in the MTI-103 study will allow for a more in-depth evaluation of the efficacy and safety profile of serlopitant in this population.

As a post-hoc analysis of the TCP-101 study suggested possible variability in baseline levels of pruritus and change over time based on gender and race, in MTI-103 randomization will be stratified by gender (male, female) and race (white, non-white).

The serlopitant 1 mg and 5 mg doses were selected for this study based on their comparable safety and efficacy profiles in the TCP-101 study. The clinical outcomes seen in TCP-101 support the previously completed human CNS PET receptor occupancy studies with serlopitant, which demonstrated higher CNS NK₁-R occupancy levels with once daily doses of 1 mg and 5 mg compared to lower doses. Analyses of dosing relative to body weight suggest that the doses selected for this study are suitable for body weights 32 kg and up.

In the completed serlopitant Phase 2 studies, over 250 subjects were exposed to serlopitant at doses and durations similar to those planned for the MTI-103 study. 41 subjects were exposed for one year. Overall, serlopitant was well tolerated. The results from MTI-103 are

expected to provide additional data regarding any potential differences in either efficacy or safety between the 1 mg and 5 mg doses.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in WI-NRS from baseline to Week 6.

3.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- WI-NRS 4-point responder rate at Week 6
- Change in ItchyQoL from baseline to Week 6

3.3.3 Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints include the following:

- WI-NRS 3-point responder rates
- Change in Average-Itch NRS (AI-NRS) and AI-NRS responder rates
- Change in 5-D Pruritus Scale
- Change in Static Patient Global Assessment of Itch Severity (sPGA)
- Change in Patient Global Impression of Change in Itch Severity (PGIC)
- Change in number of night-time scratching events per hour from baseline to Week 6

3.3.4 Safety Endpoints

Safety endpoints include the following:

- Incidence of TEAEs and 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 Investigators' Global Assessment of atopic dermatitis severity (IGA-AD)
- Change in sleep efficiency
- Change in mean activity during the sleep period

3.4 **Safety Review**

3.4.1 *Independent Data Monitoring Committee*

An independent Data Monitoring Committee (iDMC) will be established to monitor unblinded safety data on a regular basis throughout the study. The iDMC may make recommendations to the Sponsor to continue or terminate the study based upon the outcomes of the data reviews. The iDMC is not tasked with stopping the study early for success (i.e. early stopping for efficacy) or for stopping for futility. The iDMC member list and its responsibilities and processes will be described in the iDMC charter.

3.4.2 *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**

Approximately 450 adult and adolescent subjects with pruritus and a history of atopic dermatitis will be randomized into this study.

4.2 **Inclusion Criteria**

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

1. Male or female, age 13 years or older at consent/assent.
 - a. For subjects below the legal age of consent, the subject must be willing and able to provide assent and to comply with study visits and study-related requirements and his/her parent(s)/guardian(s) must be willing and able to provide written informed consent.
2. Pruritus of at least 4 weeks duration prior to the initial Screening visit and during the 2-week screening period, despite treatment with standard of care anti-pruritic therapies such as H1 antihistamines or emollients.

- a. Subjects using stable doses of oral H1 antihistamines at the initial Screening visit must be willing to continue these at the same doses and frequencies throughout the study inclusive of the follow-up period.
3. WI-NRS score ≥ 7 in the 24-hour period prior to the initial Screening visit.
4. Average weekly WI-NRS score ≥ 6 for each week of the screening period, as recorded in the eDiary.
5. Diagnosis of atopic dermatitis, as defined by the 2014 American Academy of Dermatology (AAD) Guidelines of Care for the Management of Atopic Dermatitis.¹
 - a. Subjects with active atopic dermatitis skin involvement must have had stable skin disease, defined as experiencing no disease flares, for at least 4 weeks immediately prior to randomization. Subjects using stable doses of bland emollients, topical calcineurin inhibitors, and/or low- to mid-potency topical corticosteroids at the initial Screening visit must be willing to continue these at the same doses and frequencies throughout the study.
 - b. Subjects without active atopic dermatitis skin involvement must have had a past diagnosis of atopic dermatitis, supported by written records documenting the presence of features consistent with the 2014 AAD Guidelines.
6. All female subjects who are of childbearing potential must 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 4 weeks after last dose of study drug. All fertile male subjects, with partners who are females of childbearing potential, must use condoms from randomization until 4 weeks after last dose of study drug. All subjects who are fertile males or females of childbearing potential must also refrain from sperm/egg donation starting from first dose of study drug and until 4 weeks after last dose of study drug. Please refer to [Section 7.1.5](#) for acceptable methods of contraception.
7. Weight ≥ 32 kg at the baseline visit.
8. Willing and able to complete once-daily eDiary entries within a consistent timeframe for the duration of the study.
 - a. Subjects must have $\geq 80\%$ eDiary completion rate during the screening period.
9. Judged to be in good health in the investigator's opinion.

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 or other NK₁-R antagonists (e.g. aprepitant).
2. Clearly defined etiology for pruritus other than atopic dermatitis. These include but are not limited to urticaria, psoriasis or other non-atopic dermatologic conditions, hepatic or renal disease, psychogenic pruritus, drug reaction, untreated hyperthyroidism, and infection.

3. Presence of any acute condition which may risk inducing an atopic dermatitis flare during the course of the study, such as impetigo or active herpes simplex infection.
4. Treatment with systemic corticosteroids within 4 weeks prior to randomization.
 - a. Treatment with non-systemic corticosteroids that do not involve skin application (e.g. inhaled, intranasal, or intra-articular corticosteroids) will be permitted.
5. Treatment with Class III or higher potency topical corticosteroids² or any topical anti-pruritic therapies (other than stable doses of low- or mid-potency topical corticosteroids, topical calcineurin inhibitors, or bland emollients) within 2 weeks prior to randomization.
6. Treatment with systemic therapies with recognized anti-pruritic (e.g. tricyclic antidepressants, sedatives, tranquilizers, gabapentin, marijuana or other cannabinoids, opioid receptor agonists/antagonists) or pruritic (e.g. opioids, angiotensin-converting enzyme inhibitors, cocaine, antimalarials) properties within 4 weeks prior to randomization.
 - a. Stable doses of H1 antihistamines will be permitted (see [Inclusion Criterion 2a](#))
7. For subjects using bland emollients, low- or mid-potency topical corticosteroids, topical calcineurin inhibitors, and/or oral H1 antihistamines, any clinically significant changes in dose or frequency during the screening period.
8. Treatment with systemic immunosuppressive/immunomodulatory therapies (including but not limited to phosphodiesterase-4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, interferon-gamma, or phototherapy) within 4 weeks prior to randomization.
9. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer.
10. Treatment with strong CYP3A4 inhibitors within 4 weeks prior to randomization (see [Appendix B](#)).
11. Use of an indoor tanning facility within 4 weeks prior to randomization.
12. Treatment with any investigational therapy within 4 weeks prior to randomization.
13. Allergen immunotherapy within 6 months prior to randomization.
14. Serum creatinine, total bilirubin, ALT or AST > 2x the upper limit of normal (ULN) during screening.
15. 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.
16. History of a major psychiatric condition (including major depressive disorder, bipolar disorder, or schizophrenia), suicidal ideation, or suicide attempt.
17. Known active hepatitis infection.
18. Known history of human immunodeficiency virus (HIV) infection.

19. Documented history of parasitic infection, including skin parasites such as scabies, within 12 months prior to randomization.
20. Known active parasitic infection.
21. Regular long-distance running (e.g. 10Ks, marathons) or long-distance bicycling (e.g. 30 + miles) and/or strenuous physical activity (e.g. bodybuilding) within 2 weeks prior to randomization
22. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject, including clinically significant ECG abnormalities during screening.
23. History of hypersensitivity to serlopitant or any of its components.
24. Currently pregnant or breastfeeding, or male subject with a pregnant or breastfeeding partner
25. Females of childbearing potential who are unable or unwilling to practice highly effective contraception (pregnancy prevention); fertile male subjects who are unable or unwilling to use condoms with female partners of childbearing potential.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

The study drug in this study is serlopitant 1 mg, 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).

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 and Week 4 visits, for a total of 3 bottles dispensed for subjects completing 6 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 taken orally) at bedtime on the first day of the treatment period (Study Day 1). Starting on Study Day 2, subjects will take one tablet per day taken orally at bedtime. Subjects will be instructed to take all doses at approximately the same time each day and no sooner than 2 hours before or after a meal.

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 after the first dose must be administered once daily at bedtime, no sooner than 2 hours before or after a meal. If the bedtime dose is missed, that dose should be skipped, and the following dose should be taken at bedtime of the following day. The skipped dose will be considered and documented as a missed dose.

5.6 Study Drug Discontinuation

Subjects will be discontinued from study drug treatment in the following events:

- The subject experiences a NCI CTCAE Grade 2 or higher treatment emergent AE that is assessed as likely related to study drug.
- The subject receives treatment with an excluded therapy or has a clinically significant change in dose or frequency of allowed adjunctive therapies (see [Section 5.7.3](#) for additional details regarding exceptions)
- The female subject becomes pregnant or female partner of a male subject becomes pregnant or is breastfeeding

Discontinuation from study drug treatment may also occur for any of the following reasons:

- Subject decision to discontinue study drug treatment, or subject decision to withdraw consent/assent from the study
- 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 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 an ETD visit within 7 days after their last dose of study drug in addition to a follow-up visit.

5.6.1 *Early Termination*

Early termination from the study may occur due to loss to follow-up or withdrawal of consent/assent 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).

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. 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.

Stable doses of the following therapies for pruritus and/or atopic dermatitis will be allowed as adjunctive therapies during the study:

- Low- or mid-potency topical corticosteroids
- Topical calcineurin inhibitors
- Oral H1 antihistamines
- Bland emollients
 - Per AAD recommendations, for subjects with active AD the regular application of emollients is an integral part of treatment of AD. Regular emollient use at stable doses is highly recommended for these subjects.

Subjects using any of these adjunctive therapies should maintain their regimen without clinically significant changes in dose or frequency throughout the screening, treatment, and follow-up periods.

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

5.7.2 *Excluded Therapies*

The following therapies and activities are excluded from the initial Screening visit through the follow-up period:

- NK₁-R antagonists (other than study drug)
- Systemic corticosteroids
 - Treatment with non-systemic corticosteroids that do not involve skin application (e.g. inhaled, intranasal, or intra-articular corticosteroids) will be permitted.
- Class III or higher topical corticosteroids or any topical anti-pruritic therapies (other than the allowed adjunctive therapies in [Section 5.7.1](#))
- Systemic therapies with recognized anti-pruritic (e.g. tricyclic antidepressants, sedatives, tranquilizers, gabapentin, marijuana or other cannabinoids, opioid receptor agonists/antagonists) or pruritic (e.g. opioids, angiotensin-converting enzyme inhibitors, cocaine, antimalarials) properties
 - Stable doses of oral H1 antihistamines will be permitted
- Systemic immunosuppressive/immunomodulatory therapies (including but not limited to PDE4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, interferon-gamma, or phototherapy)
- Biologic therapies
- Strong CYP3A4 inhibitors (See [Appendix B](#))
- Use of an indoor tanning facility
- Allergen immunotherapy
- Long-distance running (e.g. 10Ks, marathons) or long-distance bicycling (e.g. 100 + miles) and/or strenuous physical activity (e.g. bodybuilding)
- Any investigational therapy

5.7.3 *Use of Excluded Therapies During the Treatment Period*

Subjects who use an excluded therapy during the treatment period for treatment of atopic dermatitis or pruritus will be discontinued from study drug treatment, with the following exception:

- Subjects who require short treatment for indications other than atopic dermatitis or pruritus (up to a total of 3 days over the treatment period) with sedatives, tranquilizers, opioids, and/or topical therapies will not be required to discontinue from study drug treatment.

Similarly, subjects with clinically significant changes in the dose or frequency of allowed adjunctive therapies (low- or mid-potency topical corticosteroids, topical calcineurin inhibitors, oral H1 antihistamines, bland emollients) during the treatment period will also be discontinued from study drug treatment.

Use of any excluded therapies will be recorded for subjects who receive them.

5.8 Assignment to Treatment

5.8.1 Randomization

Eligible subjects will be randomized to receive serlopitant 1 mg, 5 mg, or placebo in a 1:1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by gender (male, female) and race (white, non-white).

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 who interact directly with investigative sites. 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. Dosing dates and times will be recorded. 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. The site staff will assess the subject's compliance with dosing by reviewing the subject's eDiary (available in the eDiary website) and the number of remaining study drug tablets relative to the number of days since the bottle was dispensed. 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. 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, both worst itch intensity (WI-NRS) and average itch intensity (AI-NRS) during a 24-hour recall period will be captured. Subjects will record their Itch NRS scores once daily via eDiary throughout the screening, treatment, and follow-up periods, as outlined in [Appendix A](#).

6.1.2 *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. Higher scores indicate greater itch severity. The sPGA scores will be captured via eDiary as outlined in [Appendix A](#).

6.1.3 *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) to (very much worse). PGIC scores will be captured via eDiary as outlined in [Appendix A](#).

6.1.4 *ItchyQoL*

ItchyQoL is a validated, pruritus-specific instrument that measures the degree to which pruritus affects quality of life (QoL).²⁹ This impact is quantified into 3 subscores (symptom, function, emotion) and an overall score. A higher score corresponds to a more adverse impact on QoL. Subjects will complete ItchyQoL as outlined in [Appendix A](#).

6.1.5 *5-D Pruritus Scale*

The 5-D Pruritus Scale is a validated, multi-dimensional measure of itching that assesses the five domains of degree, duration, direction, disability and distribution. Subjects rate their symptoms over the preceding 2-week period on a 1 to 5 scale, with 5 being the most affected. Subjects will complete the 5-D Pruritus Scale during study visits as outlined in [Appendix A](#).

6.1.6 *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 16g (0.56oz) 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 0.5m. It is functional for operation between 41 and 104 degrees Fahrenheit (5 and 40 degrees Celsius).

The assessment requires each subject to wear the actigraphy devices, which are the size of a medium size wrist watch, on each wrist during sleep, with the option to wear them during waking hours as well. 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 where the data are

downloaded and sent for analysis. Subjects will be permitted to not wear the devices up to three sleep sessions over any seven-day period throughout the study, to allow for cases of temporary irritation or discomfort.

The 3-D acceleration data (m/sec²) 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*.³⁰

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

6.1.7 *Investigators' Global Assessment of Atopic Dermatitis Severity*

The IGA-AD is an instrument used to assess the overall severity of atopic dermatitis at a given time point, as determined by the investigator. It consists of a 6-point scale ranging from 0 (clear) to 5 (very severe). The IGA-AD uses clinical characteristics of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment.³¹ IGA-AD scores will be assessed as outlined in [Appendix A](#).

6.2 *Safety Parameters*

Safety assessments will consist of monitoring and recording protocol-defined AEs and 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. 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 may be abbreviated and targeted to changes in disease activity and/or subjects' symptoms.

6.2.3 Clinical Laboratory Assessments

Samples for hematology, chemistry, urinalysis, and serum pregnancy testing (when necessary) will be collected as outlined in [Appendix A](#) and at unscheduled study visits when clinically indicated, and 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 (BUN), 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 and cardiac: TSH, free T4, cortisol, corticotropin, troponin
- Reproductive endocrine (for all female subjects): serum FSH, LH, estradiol, progesterone

6.2.4 Electrocardiogram

A standard 12-lead ECG will be performed as outlined in [Appendix A](#) and at unscheduled study visits when clinically indicated.

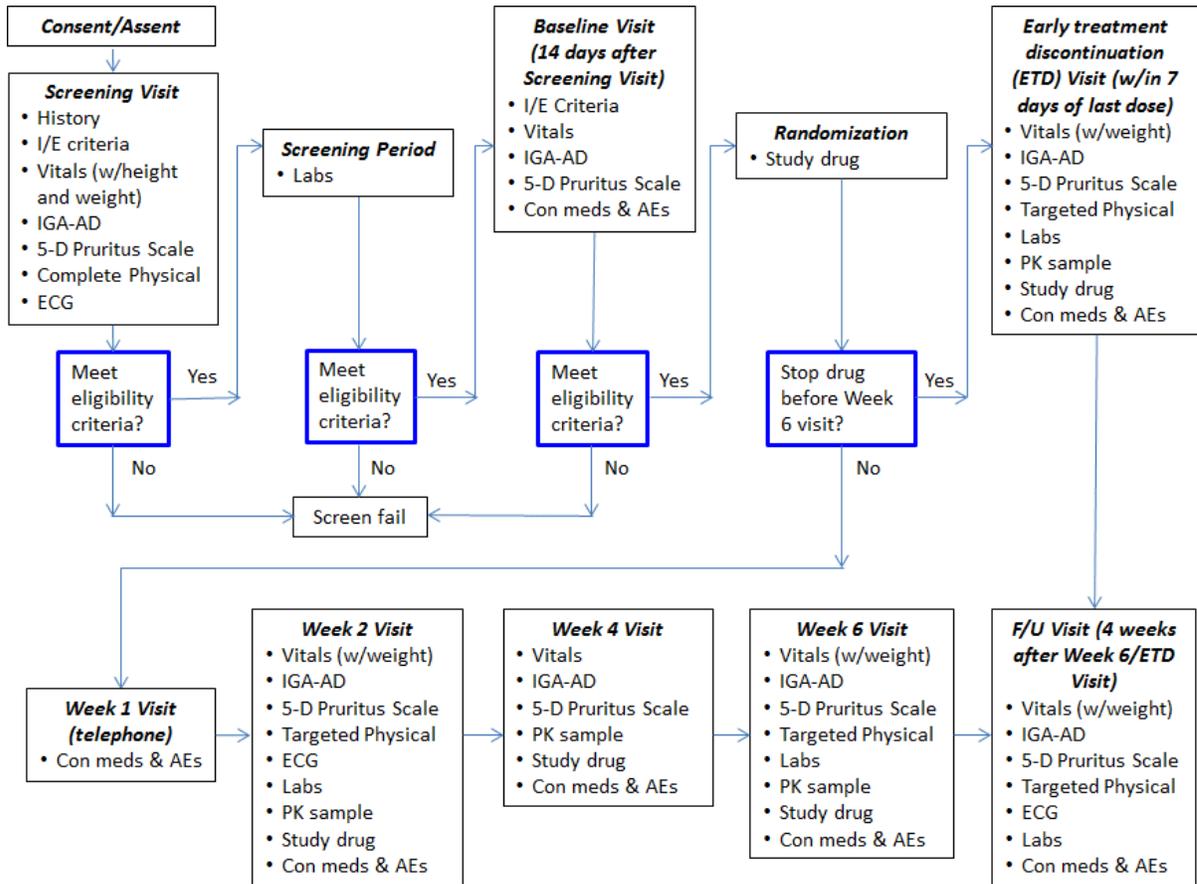
6.3 Pharmacokinetics Measurements

Sparse PK sampling will collect one PK sample at each of the Week 2, Week 4, and Week 6 visits as well as the ETD visit as outlined in [Appendix A](#). The date and time of dosing prior to PK sample collection and date and time of PK sample collection will be recorded in the eCRF. 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, 6.2, and 6.3](#).

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 Informed Consent/Assent

Informed consent will occur prior to any protocol-mandated procedures, including the stopping of any excluded therapies. This may occur prior to the initial Screening visit.

6.5.2 *Screening Visit/Period*

An initial Screening visit should be scheduled to occur 14 days (-2 days, +3 days) prior to the Baseline visit. The following screening procedures are to be performed at the initial Screening visit:

- Inclusion/exclusion criteria review
- Medical history
- Complete physical examination
- Vital signs (including height and weight)
- IGA-AD
- 5-D Pruritus Scale
- ECG
- Schedule the baseline visit
- Provide actigraphy device with instructions
- Provide eDiary with instructions

During the screening period (after consent/assent and prior to the baseline visit), the following screening procedure is to be performed:

- Laboratory
 - Reproductive endocrine labs for females
 - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
 - Endocrine and cardiac
 - Hematology
 - Chemistry
 - Urinalysis

6.5.3 *Baseline Visit*

The Baseline visit occurs 14 days (-2 days, +3 days) after the Screening visit. At the Baseline visit, the following procedures and assessments are to be performed:

- Inclusion/exclusion criteria review
- Vital signs

- IGA-AD
- 5-D Pruritus Scale
- Concomitant medications
- AEs
- Randomization if eligible
- Dispense study drug
- Schedule future visits

Randomized subjects will begin treatment with study drug in the evening of the Baseline visit (Study Day 1).

6.5.4 *Week 1 Visit*

The Week 1 visit is a telephone visit that occurs 7 days (± 3 days) after the Baseline visit (Study Day 5-11). At the Week 1 visit, the following procedures and assessments are to be performed:

- Concomitant medications
- AEs

6.5.5 *Week 2 Visit*

The Week 2 visit occurs 14 days (± 2 days) after the Baseline visit (Study Day 13-17). At the Week 2 visit, the following procedures and assessments are to be performed:

- Vital signs (including weight)
- IGA-AD
- 5-D Pruritus Scale
- Targeted physical examination
- ECG
- Laboratory
 - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
 - Hematology

- Chemistry
- Urinalysis
- PK blood sample collection
- Concomitant medications
- AEs
- Collect returned study drug
- Dispense study drug

6.5.6 *Week 4 Visit*

The Week 4 visit occurs 28 days (\pm 3 days) after the Baseline visit (Study Day 26-32). At the Week 4 visit, the following procedures and assessments are to be performed:

- Vital signs
- IGA-AD
- 5-D Pruritus Scale
- PK blood sample collection
- Concomitant medications
- AEs
- Collect returned study drug
- Dispense study drug

6.5.7 *Week 6 Visit*

The Week 6 visit occurs 42 days (\pm 3 days) after the Baseline visit (Study Day 40-46). At this visit, the following procedures and assessments are to be performed:

- Vital signs (including weight)
- Targeted physical examination
- Laboratory
 - Reproductive endocrine labs for females
 - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)

- Endocrine and cardiac
- Hematology
- Chemistry
- Urinalysis
- IGA-AD
- 5-D Pruritus Scale
- PK blood sample collection
- Concomitant medications
- AEs
- Collect returned study drug

6.5.8 *Early Treatment Discontinuation Visit*

The ETD visit occurs within 7 days of the last dose of study drug for subjects who discontinue study drug treatment early. At this visit, the following procedures and assessments are to be performed:

- Vital signs (including weight)
- Targeted physical examination
- Laboratory
 - Reproductive endocrine labs for females
 - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
 - Endocrine and cardiac
 - Hematology
 - Chemistry
 - Urinalysis
- IGA-AD
- 5-D Pruritus Scale
- PK blood sample collection
- Concomitant medications
- AEs
- Collect returned study drug

6.5.9 *Follow-up Visit*

The Follow-up visit occurs 28 days (\pm 3 days) after the Week 6 visit (Study Day 68-74) or the ETD visit (for subjects who discontinue study drug early). Subjects who discontinue study drug prior to Study Day 15 should have a follow-up visit 6 weeks (\pm 3 days) after randomization (Study Day 40-46) so that all randomized subjects will have a Week 6 evaluation. At the Follow-up visit, the following procedures and assessments are to be performed:

- Vital signs (including weight)
- Targeted physical examination
- ECG
- Laboratory
 - Reproductive endocrine labs for females
 - Urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
 - Endocrine and cardiac
 - Hematology
 - Chemistry
 - Urinalysis
- IGA-AD
- 5-D Pruritus Scale
- Concomitant medications
- AEs

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 exacerbations of pre-existing illnesses that are temporally associated with the use of study drug 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 hospitalizations 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/assent, 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 unless their severity, seriousness, or etiology changes.

7.1.4 Deaths

Any deaths that occur from the time of informed consent/assent to the follow-up visit, regardless of attribution, must be reported within 24 hours of investigator's awareness of the death. See MTI-103 SAE and Pregnancy Form Completion Instructions 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 Males and 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. A fertile male is defined as any male who is post-pubertal and not castrated (e.g. history of bilateral orchiectomy) or sterilized (i.e. history or vasectomy).

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^{32,33,34}.

1. For female subjects: All female subjects of childbearing potential must use highly effective contraception, which includes the use of one or more of the following acceptable methods:
 - a. Surgical sterilization (e.g., bilateral tubal occlusion or ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
 - b. Total (as opposed to periodic or cyclic) abstinence

- c. 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.
 - i. Progesterone only oral contraceptives are excluded as a highly effective method, as they do not consistently inhibit ovulation.
 - d. Intrauterine device/system
 - e. Exclusive monogamous heterosexual intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner
2. For male subjects: All fertile male subjects, with sexual partners who are females of childbearing potential, must use condoms with or without spermicide.
 3. All subjects who are fertile males or females of childbearing potential must also refrain from sperm/egg donation starting from first dose of study drug and until 4 weeks after last dose of study drug.

Any pregnancy occurring in a female subject or the female partner of a male subject, from the first study drug administration through the 4-week follow-up visit must be reported within 24 hours of the investigator's awareness of the pregnancy. See MTI-103 SAE and Pregnancy Form Completion Instructions 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-103 SAE and Pregnancy Form Completion Instructions for complete instructions.

7.1.6 *Worsening of Pruritus or Atopic Dermatitis*

Pruritus or atopic dermatitis 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. significant atopic dermatitis flare in previously uninvolved skin).

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 4-week follow-up visit, only SAEs that are believed to be drug-related should be reported.

After informed consent/assent, 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 SAE form, not on the AE form of the 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) v4.03³⁵ to describe the maximum intensity of the AE.

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 ^a
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 instrumentation activities of daily living (ADL) ^b
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 ^c
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	

^a 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.

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

^c 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) v4.03³⁵

Regardless of severity, some AEs may meet the criteria for seriousness. See [Section 7.1.2](#) for the definition of an SAE.

The Sponsor or designee should be notified within 24 hours of investigator’s awareness of any Grade 3 or higher AE whenever possible.

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 or Ethics Committee

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/assent 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-103 SAE and Pregnancy Form Report Completion Instructions 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 (EC). 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 AEs 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

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.

Baseline for measures other than the eDiary and actigraphy based measures, will be the last recorded value prior to the start of treatment. For Itch NRS measures, baseline will be the average result measured over 7 days prior to treatment. Additionally, the Itch NRS measures will be summarized in one week intervals by taking the average result recorded within the associated week.

8.1 Decision Rule and Sample Size

This study contains two active dosing arms. A stepdown procedure will be used to control for multiplicity. This procedure will start by testing the primary endpoint for the 5 mg treatment group and then proceed to the 1 mg group should statistical significance (one-sided p-values < 0.05) be reached for the 5 mg vs placebo comparison.

Statistical significance for the key secondary endpoints will be dependent upon statistical significance being reached for the primary endpoint at the given dose level (i.e. a gatekeeper within dose arm will be used for the secondary endpoints). As there are multiple secondary endpoints a stepdown procedure will be used starting with the WI-NRS endpoint and then the ItchyQoL.

If the one-sided p-values are additionally less than 2.5%, then the serlopitant-based regimen will have met the generally accepted level of evidence required to demonstrate efficacy.

The target sample size of 450 randomized and dosed subjects (150 per group) has been determined based upon a 1:1:1 allocation of subjects to treatment groups, an assumed common treatment effect for the 1 mg and 5 mg arms, and a 5% one-sided alpha level. One-hundred and fifty subjects per group results in 90% power for each test individually assuming a treatment effect (placebo change from baseline - serlopitant change from baseline) of -1 and a standard deviation of 2.9.

The sample size calculations have been performed in PASS 13³⁶ and use a t-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.³⁷

8.2 Handling of Missing Data and Excluded Therapy Use

For summary statistics results will generally be reported based upon observed data. Should a determination of treatment period (on treatment, pre-treatment) be required for AEs 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.

If a subject fails to complete their eDiary for a week or more, the Itch NRS endpoints, including the primary endpoint, will be missing for that week. In this case, their Itch NRS change from baseline value will be imputed. This approach uses the subject's last week with

data. From that point forward their trajectory will be imputed based upon the trajectory of their treatment group.

The imputation approach first determines the average change for each week for each treatment group. The difference in the weekly measures between weeks n-1 and n will be considered the change for Week n. These weekly change measure will be used to ‘fill in’ the missing weeks between the last completed week and Week 6.

For subjects who receive excluded therapy or with clinically significant changes in allowed adjunctive therapies as outlined in [Section 5.7.3](#), their Itch NRS results after the use of this therapy will be imputed using the same algorithm as indicated above. Hence, a placebo subject who receives excluded therapy in Week 4 will have their Week 6 WI-NRS change from baseline imputed as $\Delta_4 + \Delta_{P(4-6)}$, where Δ_4 is the observed change from baseline result for the subject up to Week 4 and $\Delta_{P(4-6)}$ is the placebo change from Week 4 to 6 (i.e. the average placebo decrease from Week 4 to 6).

As a sensitivity analysis, a similar approach will be used where the imputation step uses multiple imputation methodology.

8.3 Analysis Populations

The primary efficacy population will be the Full Analysis Set (FAS) that will include all randomized and treated subjects. Following the intent-to-treat philosophy, subjects will be analyzed within the treatment group to which they are randomized.

The primary safety population will be all treated subjects. For safety analyses, subjects will be classified based upon the treatment received.

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 (WHO) 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 recorded within the eDiary. From these entries, summaries of treatment compliance and exposure will be produced.

8.8 Efficacy Analyses

The efficacy endpoints will be summarized within the FAS using descriptive statistics by time point and treatment. For the WI-NRS and AI-NRS endpoints (change from baseline, 3-point and 4-point responders) results will be summarized at the primary time point, Week 6, as well as at Week 2 and 4. The WI-NRS and AI-NRS results will be summarized at baseline and Weeks 2, 4 and 6. For each of these measures the result at a time point are based upon the average of the results leading up to that time point. The night-time scratching events, ItchyQoL, 5-D Pruritus Scale and sPGA will also be summarized at baseline and Weeks 2, 4 and 6 with change from baseline summarized at Weeks 2, 4 and 6. Week 6 is the primary time point for the ItchyQoL. The PGIC will be summarized at Weeks 2, 4 and 6.

For the primary and key secondary endpoints these statistics will include 95% confidence intervals for the treatment difference. Testing will also be used for the primary and key secondary endpoints.

For the responder rate endpoints subjects will be considered a responder if they have at least a 3 or 4 point reduction in WI-NRS / AI-NRS between baseline and the corresponding week.

The difference in the primary efficacy outcome measure (WI-NRS change from baseline to Week 6) between treatment groups will be tested using an analysis of variance (ANOVA) model controlling for the stratification factors. A main effects model with an interaction term (treatment by stratification factors) and a Type II hypothesis will be used. More precisely this ANOVA model uses the following as a stratified adjusted measure of the change from baseline for a given treatment group:

$$\Delta = \sum_{j=1}^4 \frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}} \Delta_j,$$

where j represents the stratification cells, n is the sample size for treatment 1 and 2 and Δ_j is the change measures for stratum j .

Conceptually the hypotheses being tested are:

$$H_0: \Delta_{Placebo} \geq \Delta_{Serlopitant} \qquad H_a: \Delta_{Placebo} < \Delta_{Serlopitant}$$

where $\Delta_{Placebo}$ is the placebo change from baseline and $\Delta_{Serlopitant}$ is the similar measure for serlopitant. Each serlopitant treatment group (1 mg and 5 mg) will be compared to placebo separately.

The primary endpoint will utilize the imputation methods as outlined in [Section 8.2](#). Sensitivity analyses in which Last Observation Carried Forward, LOCF, and Baseline Observation Carried Forward, BOCF, are used will be performed. The LOCF approach assumes subject's final assessment is reflective of their future assessment and can be useful if

subjects are withdrawing due to lack of efficacy, as this lack of efficacy is carried forward. The BOCF approach for responder rate endpoints is equivalent to a missing equals failure imputation.

The differences between treatment groups for the ItchyQoL key secondary endpoint will be tested using the same analysis of variance (ANOVA) model used for the primary endpoint. A Cochran Mantel Haenszel (CMH) test controlling for the ‘as randomized’ stratification factors will be used for the responder rate key secondary endpoint.

8.9 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. In addition, a responder definition will be explored using anchor- and distribution-based methods.

8.10 Safety Analyses

8.10.1 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.

8.10.2 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.

8.10.3 Vital Signs

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

8.10.4 *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 will be provided in a listing.

8.11 *Interim Analyses*

This study includes an iDMC that will review study results to identify potential safety concerns. The iDMC is not tasked with stopping the study early for efficacy or for futility determinations.

8.12 *Pharmacokinetics Data*

The PK data and analysis for serlopitant and metabolites will be reported in a PK report that will 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 or EC:

- 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, or the recommendation of the iDMC. A written statement fully documenting the reasons for study termination will be provided to the IRB or EC.

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 or EC-approved consent form before any study-specific procedures are carried out. Subjects below the legal age of consent will be required to read, sign, and date an IRB-approved or EC-approved assent form, and his/her parent(s)/guardian(s) will be required to read, sign, and date an IRB-approved or EC-approved consent form. 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 and assent forms will be maintained in the investigator site file. Copies of signed consent/assent forms will be provided to the subject.

9.6 Communication with the Institutional Review Board or Ethics Committee

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

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

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 or EC. 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/assent 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	Consent	Screening	Baseline	Week 1	Week 2	Week 4	Week 6	ETD*	F/U**	Comments & Clarifications
Study Days (D)			D 1	D 8	D 15	D 29	D 43	*	**	
Visit Window in Days (d)			-2d, +3 d	±3 d	±2 d	±3 d	±3 d	*	±3 d	
Informed consent/assent	X									Informed consent will occur prior to any protocol-mandated procedures, including the stopping of any excluded therapies. This may occur prior to the initial Screening visit.
Medical history		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	X	Height will be assessed at screening; Weight will be assessed at screening, baseline, Week 2, Week 6, ETD, and F/U
ECG		X			X				X	
Labs		X			X		X	X	X	Screening labs, including urine pregnancy test, may be collected during the screening period (after Screening visit but prior to the Baseline visit); Endocrine and cardiac, and reproductive endocrine labs will be collected at screening, Week 6, ETD, and F/U
PK					X	X	X	X		
IGA-AD		X	X		X	X	X	X	X	
5-D Pruritus Scale		X	X		X	X	X	X	X	
Dispense study drug			X		X	X				
Collect study drug					X	X	X	X		
Concomitant medications			X	X	X	X	X	X	X	
AEs			X	X	X	X	X	X	X	After informed consent/assent, but prior to study drug administration, only SAEs caused by a protocol-mandated intervention will be collected

* Early Treatment Discontinuation (ETD) visit occurs within 7 days of last dose for subjects who discontinue study drug treatment prior to the Week 6 visit

**The Follow-up (F/U) visit occurs 28 days (± 3 days) after the Week 6 visit (Study Day 68-74) or the ETD visit (for subjects who discontinue study drug early). Subjects who discontinue study drug prior to Study Day 15 should have a follow-up visit 6 weeks (± 3 days) after randomization (Study Day 40-46) so that all randomized subjects will have a Week 6 evaluation.

APPENDIX A (CONT'D)

Table 3 Schedule of eDiary and Actigraphy Assessments

eDiary and actigraphy devices are provided to subjects at the screening visit. eDiary devices are collected at the Follow-up Visit. Actigraphy watches will be returned to site and new watches dispensed to subject as needed during the study period.

Device	Assessment	Frequency and Duration of Assessment
eDiary	WI-NRS	Once daily from Screening visit through the Follow-up visit
eDiary	AI-NRS	Once daily from Screening visit through the Follow-up visit
eDiary	ItchyQOL	Once at screening, baseline*, Week 2, Week 4, Week 6, ETD, and Follow-up visit
eDiary	sPGA	Once at screening, baseline*, Week 2, Week 4, Week 6, ETD, and Follow-up visit
eDiary	PGIC	Once at Week 2, Week 4, Week 6, ETD, and Follow-up visit
Actigraphy watch	Scratching	Continuous nighttime monitoring from Screening visit through the Follow-up visit
Actigraphy watch	Sleep	Continuous nighttime monitoring from Screening visit through the Follow-up visit

*Baseline assessments need to be done prior to initial study drug administration.

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)*³⁸:

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^a
12. ketoconazole^a
13. lopinavir and ritonavir
14. nefazodone
15. nelfinavir
16. paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
17. posaconazole^a
18. ritonavir
19. saquinavir and ritonavir
20. telaprevir
21. tipranavir and ritonavir
22. troleandomycin
23. voriconazole^a

^a Topical formulations of azoles are not considered strong CYP3A4 inhibitors due to limited systemic absorption.