A Randomized, Double-Blind, Placebo-controlled Study Of The Efficacy, Safety, And Tolerability Of Serlopitant For The Treatment Of Chronic Pruritus Of Unknown Origin

Protocol Version/Date: Version 3.0 / 11 Feb 2019

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CLINICAL STUDY PROTOCOL

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF CHRONIC PRURITUS OF UNKNOWN ORIGIN
IND No.:	117780
ClinicalTrials.gov ID:	[Placeholder]
Protocol No.:	MTI-117
Protocol Version/Date:	Version 3.0 / 11 Feb 2019
Development Phase:	Phase 2
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063 USA

Confidentiality Statement:

SIGNATURE PAGE FOR INVESTIGATOR(S)

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I have read the protocol and agree to conduct this study in accordance with the protocol, all relevant laws and regulations in force at the time, International Council 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)

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

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Approved by:

PPD

PPD

11 Feb 2019

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 Chronic Pruritus of Unknown Origin
Protocol Number:	MTI-117
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 2
Study Objectives:	Primary objective: To assess the efficacy of repeated oral doses of serlopitant in adult subjects with chronic pruritus of unknown origin. Secondary objective: To assess the safety and tolerability of repeated oral doses of serlopitant in adult subjects with chronic pruritus of unknown origin.
Study Design:	This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of chronic pruritus of unknown origin. Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 5-week follow-up period. The study will consist of three periods, for a total study period of 18 weeks: • Screening period: 3 weeks • Treatment period: 10 weeks • Follow-up period: 5 weeks Informed consent will occur prior to any protocol-mandated procedures, including the stopping of any excluded therapies. This may occur prior to the Screening visit. During the screening period, all subjects will undergo eligibility evaluation and will be assessed for conditions associated with chronic pruritus. If the investigator deems that additional assessments are necessary to rule out specific conditions based on a subject's history, physical examination, and/or screening labs (e.g. scabies skin preparations, urea breath test for *Helicobacter pylori*), the subject may not be randomized until these are completed and the pruritus is still considered to be of unknown origin. Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study. At the Baseline visit (Day 1), eligible subjects will be randomly assigned to receive study drug (serlopitant 5 mg or placebo). Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Day 1). Starting on Day 2, subjects will take one tablet per day until the completion of the 10-week treatment period. Study drug may be taken with or without food. After the last dose of study drug, all subjects will enter a 5-week follow-up period and will undergo a follow-up visit at the conclusion of the follow-up period. The primary efficacy endpoint will be assessed at Week 10 of treatment.

Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor blinded safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 200 subjects will be randomized in a 1:1 distribution. Randomization will be stratified by age and baseline WI-NRS scores. Randomization of subjects < 50 years of age will be capped at 25% of the total randomized population. This cap may be increased up to 33% of the total randomized population at the Sponsor's discretion based on relative enrollment rates.
Study Population:	The study will consist of adult subjects with chronic pruritus of unknown origin. Inclusion Criteria (Subjects must meet the following criteria to be randomized into the study): 1. Male or female, age 18 years or older at consent. 2. The subject must have had ongoing pruritus for at least 6 months. 3. The subject's pruritus is assessed by the investigator to be of unknown origin at baseline. 4. The pruritus must have been unresponsive to prior treatment with emollients. 5. The pruritus must involve more than one dermatome (defined as an area of skin in which sensory nerves derive from a single spinal nerve root). Acceptable examples include right and left arm, occipital and frontal scalp, and upper and lower back. 6. Worst-Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the 24-hour period prior to the Screening visit 7. Average weekly Worst Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the week (7 days) immediately prior to randomization, as recorded in the eDiary. 8. Willing and able to complete daily eDiary entries within a consistent timeframe for the duration of the study, as demonstrated by a ≥ 80% eDiary completion rate in the two weeks immediately prior to randomization. 9. All females who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last study dosing. 10. Adequate cognitive and physical ability, in the investigator's opinion, to comply with study visits and study related requirements including providing written informed consent. Exclusion Criteria (Subjects who meet any of the following criteria are not eligible for participation in the study): 1. Prior treatment with serlopitant or any other neurokinin-1 receptor antagonist. 2. Known dermatologic or systemic condition(s), other than dry skin, that is considered by the investigator to be the primary cause of current pruritus.

	3. Untreated or inadequately treated thyroid, adrenal, or pituitary disease or nodules, or history of thyroid malignancy. 4. Use of an excluded therapy within 3 weeks prior to randomization (see Section 5.7). 5. Treatment with any investigational therapy within 3 weeks prior to randomization. 6. Serum creatinine, total bilirubin, alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal during screening. 7. History of malignancy within 3 years prior to randomization, with the exception of actinic keratosis or completely treated and non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma of the skin. 8. Any known major psychiatric diagnosis which, in the investigator's opinion, may confound the assessment of serlopitant safety or efficacy or interfere with the subject's ability to comply with protocol-mandated activities. 9. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt. 10. Known use of recreational drugs. 11. Documented history of parasitic infection, including skin parasites such as scabies, within 12 weeks prior to randomization. 12. Presence of clinically significant dementia, intellectual impairment, or 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. 13. History of hypersensitivity to serlopitant or any of its components. 14. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g. extended international travel) during the subject's participation in the study. 15. Pregnant or breastfeeding female.
Study Drug:	Serlopitant 5 mg oral tablets and matching placebo.
Dosage:	Serlopitant: 5 mg once daily by mouth for 10 weeks, following a 3-tablet (15 mg) loading dose on the first day of the treatment period. Matching placebo: Once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period.
Primary Efficacy Endpoint:	The primary efficacy endpoint is the WI-NRS 4-point responder rate at Week 10.
Secondary Efficacy Endpoints:	The secondary efficacy endpoints are as follows: • WI-NRS 4-point responder rate at Weeks 2, 4, 6, and 8 • WI-NRS 3-point responder rate at Weeks 2, 4, 6, 8, and 10 • Change from baseline in WI-NRS at Weeks 2, 4, 6, 8, and 10 • Change from baseline in daily WI-NRS scores through Week 2 • Change from baseline in WI-VAS at Weeks 2, 4, 6, and 10

Safety Endpoints:	Safety endpoints are as follows: • Incidence of treatment-emergent adverse events and serious adverse events (SAEs) • Changes from baseline in clinical laboratory parameters following study drug exposure • Changes from baseline in vital sign and electrocardiogram (ECG) parameters following study drug exposure • Plasma concentrations of serlopitant and metabolites
Exploratory Endpoints:	The exploratory endpoints are as follows: • Change from baseline in the Epworth Sleepiness Scale (ESS) to Weeks 2, 4, 6, and 10 • Change from baseline in Static Patient Global Assessment of Itch Severity (sPGA) to Weeks 2, 4, 6, and 10 • Patient Global Impression of Change in Itch Severity (PGIC) at Weeks 2, 4, 6, and 10
Decision Rule and Sample Size:	This study will use a 5% one-sided alpha level. The target sample size of 200 randomized and dosed subjects (100 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. Two hundred subjects results in at least 90% power assuming a placebo 4-point responder rate of CCI% and a serlopitant 4-point responder rate of more than CCI%.
Statistical Methods:	Efficacy analyses will be based upon an intent-to-treat philosophy. The primary efficacy population will be the full analysis population that will include all randomized subjects who were dispensed study drug. Subjects will be analyzed within the treatment group to which they are randomized. Efficacy Analyses: The primary efficacy endpoint is a binary variable taking on values of responder or non-responder. Subjects will be considered a responder if they have at least a 4-point reduction in WI-NRS from baseline to Week 10. Missing data imputation will be used for subjects who fail to complete the eDiary at Week 10, unless the subject withdrew from the study due to a lack of efficacy, or the subject used rescue therapy (i.e. an excluded therapy to treat worsening of pruritus), in which case their responder status will be defined as non-responder. The primary endpoint will be summarized with descriptive statistics by treatment group and study week. The difference in the primary efficacy outcome measure between treatment groups will be tested using a Cochran Mantel Haenszel test controlling for the stratification factors. Testing of selected secondary efficacy endpoints will also be employed.

	Safety Analyses: 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. 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. 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. 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. The overall ECG assessment (abnormal or normal) will be summarized along with a summary of how many subjects developed a post treatment abnormal result.
Study Sites:	Approximately 40 study sites
Expected Duration of Subject's Participation	18 weeks: 3 weeks of screening, 10 weeks of treatment, and a follow-up period of 5 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone, corticotropin
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CMH	Cochran Mantel Haenszel test
CNS	Central Nervous System
CPUO	Chronic Pruritus of Unknown Origin
CRO	Contract Research Organization
CYP3A4	Cytochrome P450 3A4
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ESS	Epworth Sleepiness Scale
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LFC	Liquid filled capsule
LH	Luteinizing hormone
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor
NOAEL	No observed adverse effect level
NRS	Numeric Rating Scale
PET	Positron Emission Tomography
PI	Principal Investigator
PD	Pharmacodynamics

PDE-4	Phosphodiesterase-4
PK	Pharmacokinetics
PN	Prurigo nodularis
PP	Per Protocol
QOL	Quality of life
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale
WI-VAS	Worst-Itch Visual Analog Scale

1 INTRODUCTION

1.1 Chronic Pruritus of Unknown Origin

Pruritus, or itch, is defined as an unpleasant sensation that elicits the desire or reflex to scratch (Ikoma 2006). Scratching can result in removal of the epidermal and dermal layers of the skin, which is thought to be an evolutionary mechanism to dislodge potential parasites. Itch is also caused by many dermatological and systemic diseases that can produce a type of pruritus that can become chronic and debilitating (Hoon 2015). Epidemiological studies indicate that point prevalence for chronic pruritus range from 13% to 17%, with lifetime prevalence of 22% to 26% (Carr 2014). Pruritus can have a substantial negative effect on quality of life, including effects on "mood, concentration, eating habits, sexual function, and sleep," (Carr 2014) and chronic pruritus has been shown to have an impact on quality of life similar to that of chronic pain (Kini 2011).

Chronic pruritus may be associated with a variety of underlying conditions, including both dermatological and systemic diseases. Many of these conditions present with visible skin involvement, such as in atopic dermatitis. Others may be associated with pruritus in the absence of visible skin involvement, such as in Hodgkin's disease. However, in 8–15% of patients with chronic pruritus, an underlying etiology cannot be identified (Weisshaar 2012). Terms in the scientific literature that have been used to describe this population include generalized pruritus of unknown origin, chronic idiopathic pruritus, and chronic itch of undetermined origin (Millington 2018, Xu 2016, Weisshaar 2009). Epidemiological studies have also shown that the prevalence of chronic pruritus increases with age (Ständer 2010), and the term chronic pruritus in the elderly has been used synonymously to describe elderly patients who present with no overt identified cause of pruritus, representing both a significant proportion of pruritus burden in the elderly, as well as a source of frustration for the affected patient and the treating physician alike (Ständer 2007, Berger 2013).

Emerging evidence indicates that the aging process itself may be involved as a primary etiologic factor in chronic pruritus in the absence of other overt causes. Xerosis and other changes in skin barrier function, increasing sensorineural dysfunction, and senescent changes in the immune system have been implicated as contributory factors (Berger 2011, Shevchenko 2018, Xu 2016). It is likely that chronic pruritus of unknown origin and chronic pruritus in the elderly represent significantly overlapping populations, especially as the age range of 51–60 years is one of the peak age ranges associated with a lifetime prevalence of chronic pruritus (Matterne 2011).

As the management of chronic pruritus is dependent on treatment of any underlying disease, chronic pruritus in the absence of an identified underlying disease or chronic pruritus in which the aging process itself may be the primary causal factor can make treatment of pruritus in these patients extremely challenging. No drugs are currently approved in the US for the primary treatment of pruritus, and off-label use of available therapies such as H1 antihistamines, gabapentin, and immunosuppressants such as corticosteroids and biologics can require significant trade-offs in terms of efficacy, tolerability, safety, and cost (Weisshaar 2012). Issues with tolerability and safety are often magnified in management of chronic pruritus with advancing age (Pereira 2018).

1.2 Substance P and the Neurokinin-1 Receptor

Substance P is an undecapeptide that belongs to the tachykinin family of neuropeptides, a group that also includes neurokinin A and neurokinin B (Hökfelt 2001). SP has been implicated in a number of biological functions, both physiological and pathophysiological, including pruritus perception, vomiting reflex, pain perception, and immunomodulatory responses (Lotts 2014, Andoh 1998, Steinhoff 2014). The biological actions of SP are mediated by tachykinin receptors, which consist of seven hydrophobic transmembrane domains coupled to G-proteins. Three tachykinin receptors have been identified: the neurokinin-1, neurokinin-2, and neurokinin-3 receptors (Harrison 2001). The neurokinin-1 receptor (NK_1 receptor) in particular has been studied in great detail. The NK_1 receptor is the primary receptor for SP in the human body, and is found on multiple cell types, include neurons in the central and peripheral nervous system and keratinocytes in the skin.

NK_1 receptor stimulation has been shown to be an important pathway for pruritus perception (Ständer 2015). Inhibition of this pathway results in decreased pruritus and scratching reflexes in animal models (Akiyama 2015). Preceding the development of serlopitant for pruritus-related conditions, a commercially available NK_1 receptor antagonist (Emend USPI) has been used as a therapy to decrease pruritus in patients with chronic pruritus due to etiologies such as cutaneous T-cell lymphoma (Duval 2009, Torres 2012, Booken 2011) and erlotinib-induced pruritus (Santini 2012, Gerber 2010). Additionally, in a study of 20 patients with chronic pruritus of various etiologies treated with aprepitant, 16/20 patients (80%) experienced a considerable reduction of itch intensity (Ständer 2010).

1.3 Serlopitant

1.3.1 Serlopitant Background and Nonclinical Summary

Serlopitant is a small molecule, highly selective NK_1-R antagonist that is administered orally and metabolized by cytochrome P-450 3A4 (CYP3A4), with a plasma half-life of 45−86 hours. It binds with high affinity to the human NK_1-R with a dissociation constant (Kd) of 46 pM; displacing SP binding with a half-maximal inhibition concentration (IC_{50}) of 61 pM. Serlopitant is a potent functional antagonist of SP-induced inositol phosphate generation.

Serlopitant has been extensively studied in animal toxicology studies, including chronic toxicology and carcinogenicity studies. In non-clinical chronic toxicology studies in rats, mice and dogs, treatment related findings of potential clinical significance included increased salivation, decreased body weight gain and food consumption, slight changes in hematology and serum biochemistry parameters, mild increases in liver weight and mild histomorphologic changes. The histomorphologic changes were seen only in rats (not in dogs or mice) and included: very slight ovarian interstitial cell hypertrophy, mammary gland and uterine atrophy; decreased corpora lutea; increased histiocytes in lung and mesenteric lymph nodes; slight skeletal and cardiac muscle degeneration; slight increased hematopoiesis in bone marrow; and slight to moderate vacuolation in kidney tubules. These nonclinical findings occurred at systemic exposures exceeding those anticipated to provide efficacy of serlopitant for pruritus indications in humans (1 to 5 mg tablet daily). No cardiac lesions have

been observed in dog toxicity studies up to 9 months in duration nor in a 3-month mouse range-finding study and 2-year mouse carcinogenicity study at exposure higher than the lowest level which caused cardiotoxicity in rats. The no observed adverse effect level (NOAEL) in rats for histomorphological changes in the reproductive tract, mammary gland and bone marrow provides a 2.5-fold margin for the maximum-targeted exposure (5 mg tablet daily). The rat NOAEL for histomorphological changes in muscle and kidney provides a 5-fold margin for the maximum-targeted exposure (5 mg tablet daily).

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

1.3.2 Serlopitant Clinical Summary

In humans, serlopitant has been administered to over 1500 individuals. Single doses up to 400 mg have been well tolerated in young adult males and single doses up to 25 mg have been well tolerated in the elderly. Multiple doses of up to 50 mg a day for 4 weeks have been well tolerated in healthy young 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 adult males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young adult and elderly subjects. A single loading dose of up to 15 mg serlopitant followed by 6 to 8 weeks of up to 5 mg daily serlopitant doses has been well tolerated in adults with chronic pruritus and prurigo nodularis.

Pharmacokinetic data demonstrate good plasma exposures with oral dosing, linear dose-dependent increases in plasma concentration and systemic exposure, a plasma $t_{1/2}$ supportive of once daily dosing, and mild effects of concomitant food ingestion. Central nervous system (CNS) positron emission tomography (PET) studies have demonstrated good CNS penetrance and > 90% NK1 receptor occupancy (RO) at plasma exposures anticipated to be safe and well tolerated. Three long-lived active hydroxylated metabolites are observed in humans: M1/M1a (L-001256771), M2/M2a (L-001194442), and M3 (L-001426583). These metabolites were present at lower concentrations and were 2- to 9-fold less potent *in vivo* than the parent compound. The integrated pharmacokinetic/pharmacodynamic (PK/PD) analysis concluded that these metabolites are unlikely to contribute significantly to occupancy of the CNS NK_1-R in humans.

1.3.3 Serlopitant in Pruritus-Related Studies

Serlopitant has been evaluated in two completed Phase 2 studies of subjects with chronic pruritus (TCP-101 and TCP-102). Three additional Phase 2 studies in pruritus indications (history of atopic dermatitis, epidermolysis bullosa, and psoriasis) are clinically complete with study reports pending.

TCP-101

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

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

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

TCP-102

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

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

also significant, -0.9. In a post-hoc analysis, 25.0% of placebo subjects and 54.4% of serlopitant subjects were 4-point responders on average VAS at Week 8.

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

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

The results of the Phase 2 studies in subjects with PN and in subjects with chronic pruritus, together with the extensive safety experience with serlopitant to date and the scientific rationale for NK_1-R inhibition in the treatment of pruritus, serve to support further evaluation of serlopitant for the treatment of chronic pruritus of unknown origin.

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

2 STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of repeated oral doses of serlopitant in adult subjects with chronic pruritus of unknown origin.

The secondary objective of this study is to assess the safety and tolerability of repeated oral doses of serlopitant in adult subjects with chronic pruritus of unknown origin.

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 chronic pruritus of unknown origin. Approximately 200 subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 5-week follow-up period.

This study will consist of three periods, for a total study period of 18 weeks:

- Screening period: 3 weeks
- Treatment period: 10 weeks
- Follow-up period: 5 weeks

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

During the screening period, all subjects will undergo eligibility evaluation and will be assessed for conditions associated with chronic pruritus. If the investigator deems that additional assessments are necessary to rule out specific conditions based on a subject's history, physical examination, and/or screening labs (e.g. scabies skin preparations, urea breath test for *Helicobacter pylori*), the subject may not be randomized until these are completed and the pruritus is still considered to be of unknown origin.

Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent 6-hour timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study. eDiary compliance and WI-NRS scores will be used to determine study eligibility (see Section 4.1).

At the Baseline visit (Day 1), eligible subjects will be randomly assigned to receive study drug (serlopitant 5 mg or placebo). Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Day 1). Starting on Day 2, subjects will take one tablet per day until the completion of the 10-week treatment period. Study drug may be taken with or without food.

After the last dose of study drug, all subjects will enter a 5-week follow-up period and will undergo a follow-up visit at the conclusion of the follow-up period. The eDiary will continue to be completed during the follow-up period.

The primary efficacy endpoint will be assessed at Week 10 of treatment.

3.2 Rationale for Study Design and Dose Selection

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

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

The current MTI-117 study is designed to investigate the efficacy, safety, and tolerability of serlopitant for the treatment of chronic pruritus of unknown origin. The 5 mg dose of serlopitant was selected for this study based on a combination of human central nervous system positron emission tomography receptor occupancy (RO) data for serlopitant generated in healthy young males (Study P002), which showed a serlopitant 4 mg LFC (equivalent to a 5 mg tablet) once daily dose is likely to achieve ~ 94% NK_1 RO at steady state, together with results of studies TCP-101 and TCP-102 that demonstrated a favorable efficacy, safety, and tolerability profile of serlopitant at this dose level in subjects with pruritus. Over 250 subjects have been exposed to serlopitant at doses of 5 mg tablet-equivalent daily for at least 6 weeks, and ~ 40 subjects have been exposed up to one year.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the Worst-Itch Numeric Rating Scale (WI-NRS) 4-point responder rate at Week 10.

3.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- WI-NRS 4-point responder rate at Weeks 2 4, 6, and 8
- WI-NRS 3-point responder rate at Weeks 2, 4, 6, 8, and 10
- Change from baseline in WI-NRS at Weeks 2, 4, 6, 8, and 10
- Change from baseline in daily WI-NRS scores through Week 2
- Change from baseline in WI-VAS at Weeks 2, 4, 6, and 10

3.3.3 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs and SAEs
- Changes from baseline in clinical laboratory parameters following study drug exposure
- Changes from baseline in vital sign and ECG parameters following study drug exposure
- Plasma concentrations of serlopitant and metabolites

3.3.4 Exploratory Endpoints

The exploratory endpoints are as follows:

- Change from baseline in the Epworth Sleepiness Scale (ESS) to Weeks 2, 4, 6, and 10
- Change from baseline in Static Patient Global Assessment of Itch Severity (sPGA) to Weeks 2, 4, 6, and 10
- Patient Global Impression of Change in Itch Severity (PGIC) at Weeks 2, 4, 6, and 10

3.4 Safety Review

3.4.1 Safety Monitoring Team

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

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 200 adult subjects with chronic pruritus of unknown origin will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. The subject must have had ongoing pruritus for at least 6 months.
3. The subject's pruritus is assessed by the investigator to be of unknown origin at baseline.
4. The pruritus must have been unresponsive to prior treatment with emollients.
5. The pruritus must involve more than one dermatome (defined as an area of skin in which sensory nerves derive from a single spinal nerve root). Acceptable examples include right and left arm, occipital and frontal scalp, and upper and lower back.
6. Worst-Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the 24-hour period prior to the Screening visit
7. Average weekly Worst Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the week (7 days) immediately prior to randomization, as recorded in the eDiary.
8. Willing and able to complete daily eDiary entries within a consistent timeframe for the duration of the study, as demonstrated by a ≥ 80% eDiary completion rate in the two weeks immediately prior to randomization.

9. All females who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last study dosing.
10. Adequate cognitive and physical ability, in the investigator's opinion, to comply with study visits and study related requirements including providing written informed consent.

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 any other neurokinin-1 receptor antagonist.
2. Known dermatologic or systemic condition(s), other than dry skin, that is considered by the investigator to be the primary cause of current pruritus .
3. Untreated or inadequately treated thyroid, adrenal, or pituitary disease or nodules, or history of thyroid malignancy.
4. Use of an excluded therapy within 3 weeks prior to randomization (see Section 5.7)
5. Treatment with any investigational therapy within 3 weeks prior to randomization.
6. Serum creatinine, total bilirubin, alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal during screening.
7. History of malignancy within 3 years prior to randomization, with the exception of actinic keratosis or completely treated and non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma of the skin.
8. Any known major psychiatric diagnosis which, in the investigator's opinion, may confound the assessment of serlopitant safety or efficacy or interfere with the subject's ability to comply with protocol-mandated activities.
9. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt.
10. Known use of recreational drugs.
11. Documented history of parasitic infection, including skin parasites such as scabies, within 12 weeks prior to randomization.
12. Presence of clinically significant dementia, intellectual impairment, or 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.
13. History of hypersensitivity to serlopitant or any of its components.
14. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g. extended international travel) during the subject's participation in the study.
15. Pregnant or breastfeeding female.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

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

The study drug will be provided in bottles for storage at room temperature (59–86°F, 15−30°C).

Each bottle provided will include 18 tablets. One bottle will be issued via Interactive Web Response System (IWRS) at each of Baseline, Week 2, and Week 4, and two bottles will be issued via IWRS at Week 6. A total of 5 bottles will be dispensed to subjects completing 10 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 the site on the first day of the treatment period (Study Day 1). Starting on Study Day 2, subjects will be instructed to take one tablet per day orally until completion of the 10-week treatment period. Study drug may be taken with or without food.

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

Each dose of study drug after the first dose must be administered as a single tablet daily. If a dose is missed, that dose will be documented as a missed dose. Dosing should resume the next day as only a single tablet, as per protocol dosing instructions (i.e. there should be no attempt to make up for the missed dose).

5.6 Study Drug Discontinuation

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

- A female subject desires to become pregnant at the current time, stops contraception or expels her intrauterine device/implant, or becomes pregnant
- A female subject has new breast findings (e.g. a palpable mass or abnormal mammography, discharge), or has abnormal vaginal discharge or bleeding
- The subject decides to discontinue study drug treatment, or withdraws consent from the study
- The subject receives a strong CYP3A4 inhibitor (See Appendix B)
- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion; this may include the development of persistently (2 successive occasions) abnormal thyroid function tests (TSH >10, or TSH > 6 with low free T4; TSH < 0.1, or TSH < 0.35 with high free T4); abnormal morning prolactin, cortisol, or corticotropin levels; or signs and symptoms of adrenal insufficiency
- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion, including evidence that the subject does not meet inclusion/exclusion criteria intended primarily for safety reasons, or a persistent lack of adherence to study procedures

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 enter a 5-week follow-up period following the last dose of study drug and will have a Follow-up visit (see Section 3.1, Section 6.5.10). Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued from study drug.

5.7 Prior, Concomitant, and Excluded Therapies

Prior therapies (including over-the-counter medications) used to treat chronic pruritus of unknown origin within the prior 3 months, including those used during the screening period, will be recorded for each subject at the Baseline visit.

Concomitant therapies include any therapies (including over-the-counter medications and bland emollients) 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. The use of

any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements, emollient use, and routine preventative immunizations.

All therapies that will be continued as concomitant therapies should be captured in source documents within 1 week of the Screening visit.

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.

Use of gentle cleansers and bland emollients (including those with urea) is encouraged for all subjects. If bland emollient use is elected, it must be initiated at least 3 weeks (21 days) prior to Baseline visit and continued throughout the treatment period.

Maintenance allergy immunotherapy will be allowed.

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

Leukotriene inhibitors will be allowed for treatment of conditions other than chronic pruritus of unknown origin (e.g. asthma).

5.7.2 Excluded Therapies

The following therapies and activities are excluded from 3 weeks prior to randomization through the treatment and follow-up periods:

- NK_1 receptor antagonists (other than study drug)
- Systemic or topical immunosuppressive/ immunomodulatory therapies (including but not limited to corticosteroids, PDE-4 inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, thalidomide, interferon-gamma, phototherapy). Build-up allergy immunotherapy will be excluded.
- Any medications that, in the investigator's and/or medical monitor's opinion, are suspected of having a causal or contributory role in the subject's pruritus.
- Biologic therapies (other than therapies such as insulins, vaccines)
- Strong CYP3A4 inhibitors (See Appendix B)
- Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn
- Any investigational therapy

The following therapies and activities are excluded from 3 weeks prior to randomization through the treatment period. Use is discouraged, though permitted, in the follow-up period:

- Topical therapies or emollients with anti-pruritic properties (including but not limited to anti-histamines, menthol or menthol derivatives, polidocanol, camphor, pramoxine, cannabinoids, colloidal oatmeal baths, and capsaicin)
- Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists)

Use of any excluded therapies (including those for the treatment of pruritus, or as rescue therapy) should be reported as soon as possible, and will be recorded as protocol deviations for subjects who receive them.

5.7.3 Rescue Therapies

The initiation of non-study drug therapy to treat worsening of pruritus is strongly discouraged throughout the treatment period. However, should rescue therapy be required for the safety and well-being of the subject, such use will be recorded and analyzed (see Section 8.2). The subject may remain on study drug, unless the rescue therapy is an NK_1 receptor antagonist, a systemic biologic therapy, a strong CYP3A4 inhibitor, an investigational therapy, or any therapy that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion.

5.8 Assignment to Treatment

5.8.1 Randomization

At the baseline visit eligible subjects will be randomized to receive serlopitant 5 mg or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by the subject's reported WI-NRS score for the 1-week period prior to the Baseline visit (7 to < 8.5, 8.5 to 10), and by the subject's age at the Baseline visit (18 to < 50 years, ≥ 50 years).

Randomization of subjects < 50 years of age will be capped at 25% of the total randomized population. This cap may be increased up to 33% of the total randomized population at the Sponsor's discretion based on relative enrollment rates.

An IWRS will be used to perform the randomization.

5.8.2 Blinding

This study will be conducted as a double-blind study with the treatment assignment concealed from the subjects, the investigators and their staff, the Sponsor, and any designees of the Sponsor as required. The placebo will be formulated to be indistinguishable from the active study product. Study materials will be packaged and issued in a manner designed to

maintain the blind for subjects and all study personnel involved in the direction and execution of study procedures, study assessments, and collection of data. The randomization code for each subject will be available to the sites for use only in an emergency situation. For details of the procedure for unblinding of individual subjects in cases of emergency see Section 7.6.

5.9 Treatment Compliance

Records of study drug used, dosages administered, and intervals between visits will be kept during the study. Subjects will 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. Study site staff will also regularly review eDiary-based study drug compliance records throughout the study. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

6 STUDY SCHEDULE AND ASSESSMENTS

When applicable, efficacy and safety instruments will be provided with instructions for administration, in study-specific manuals for site reference.

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. The questionnaire is provided in Appendix C.

During the study, WI-NRS assessments will be reported by the subject via eDiary. Subjects will record their WI-NRS scores once daily at approximately the same time each day (+/- 3 hours) throughout the screening, treatment, and follow-up periods, as outlined in Appendix A. Subjects may be allowed to adjust the timing of eDiary completion within the first week of Screening as needed. Standardized training and instructions will be provided to all subjects prior to eDiary use.

6.1.2 Itch Visual Analog Scale

The Itch VAS 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 worst itch on a 100-mm horizontal line ranging from 0 mm (no itch) to 100 mm (worst itch imaginable). Higher scores indicate greater itch intensity. The VAS measurement will be summarized in centimeters. Standardized paper questionnaires will be distributed to sites and, in order to ensure consistency, cannot be copied, printed, or faxed.

During the study, WI-VAS assessments will be reported by the subject via a paper form administered at study visits. Standardized training and instructions will be provided to all subjects prior to administration of the WI-VAS assessments.

6.1.3 Static Patient Global Assessment of Itch Severity

The Static Patient Global Assessment of Itch Severity (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 on paper according to the schedule in Appendix A.

6.1.4 Patient Global Impression of Change in Itch Severity

The Patient Global Impression of Change in Itch Severity (PGIC) 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 on paper according to the schedule in Appendix A.

6.1.5 Epworth Sleepiness Scale

The ESS is a QOL instrument intended to measure daytime sleepiness by use of a very short questionnaire (8 items each scored from 0–3). The ESS score can range from 0 to 24. Higher scores indicate greater daytime sleepiness. The questionnaire takes approximately 2 to 3 minutes to complete, and is provided in Appendix D. The ESS questionnaire will be collected as outlined in Appendix A.

6.2 Safety Parameters

Safety assessments will consist of monitoring and recording AEs and SAEs, vital signs, physical examinations, clinical laboratory assessments, ECGs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug according to the schedule in Appendix A.

6.2.1 Vital Signs

Vital signs will include measurements of heart rate, blood pressure, respiration rate, and temperature after the subject has been calmly resting (seated or supine) for a minimum of 5 minutes. Vital signs will be assessed according to the schedule in Appendix A and at unscheduled study visits when clinically indicated. On study visits when clinical laboratory tests are performed, assessment of vital signs should precede blood draw.

6.2.2 Physical Examination

Physical examinations, including height and weight measurements, will be performed according to the schedule in Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the screening visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity

and/or subjects' symptoms. If targeted breast examinations are to be performed in female subjects, please perform breast examination after blood draw for clinical laboratory tests.

6.2.3 Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected according to the schedule 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, and are ideally performed in the morning, particularly at visits with endocrine assessments (Screening, Week 10, and Follow-up):

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, uric acid, total protein, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel
- Iron studies: ferritin, serum iron
- Serology: hepatitis B and C serology, HIV
- Serum IgE
- 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
- Endocrine: TSH, free T4, cortisol, corticotropin (adrenocorticotropic hormone, ACTH), prolactin
- Reproductive endocrinology (for all female subjects under 55 years of age at consent, who are not using hormonal contraception or other hormonal therapies at Screening): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)
- Optional study provided in lab test kits for use at Screening only: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis
- Additional optional studies deemed necessary by the investigator to rule out specific conditions associated with chronic pruritus based on a subject's history, physical examination, and/or screening labs may be performed; the investigator should discuss the need for such studies with the medical monitor during the Screening period.

- Standard cosyntropin stimulation testing should be performed on subjects with low cortisol level (i.e. < 3.0 mcg/dL); the investigator should discuss low cortisol (and relevant low corticotropin) results with the medical monitor.

6.2.4 Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been calmly resting in a supine position for a minimum of 5 minutes before obtaining the ECG. ECGs should precede measurement of vital signs and blood draw for clinical laboratory tests and will be performed according to the schedule in Appendix A and at unscheduled study visits when clinically indicated. ECGs will be read centrally. The ECG machine and detailed instructions will be provided by the ECG vendor.

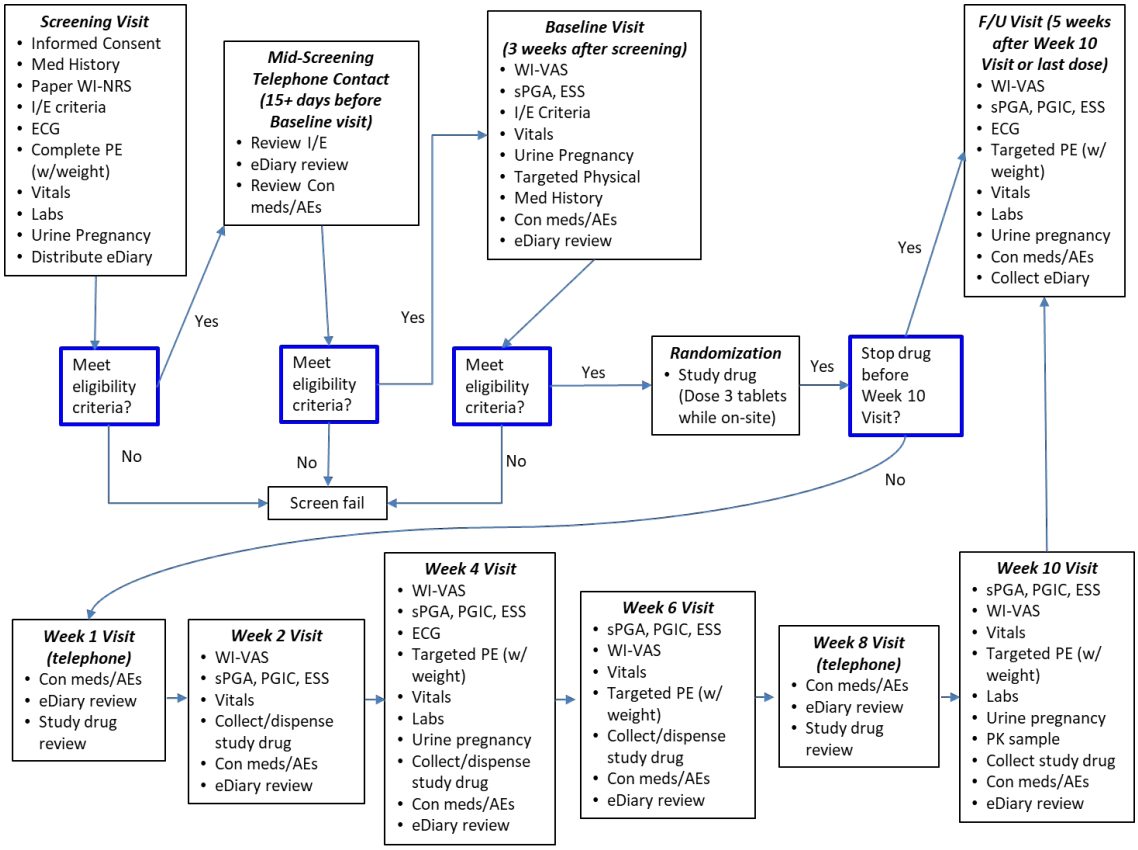
6.3 Pharmacokinetic Measurements

Sparse PK sampling will involve collecting one PK sample at the week 10 visit according to the schedule 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. The plasma concentrations of serlopitant and metabolites M1/M1a, M2/M2a and M3 will be determined and data used for population PK analysis. Detailed instructions regarding PK sample collection, preparation, and shipment can be found in the laboratory manual.

6.4 Subject Flow Diagram

The visit schedule and assessments are summarized in Appendix A. The following subject flow diagram provides a summary of assessments and decision points for each subject. The eDiary assessments are performed throughout the study and are not confined to scheduled visits.

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. The timing of each study visit is relative to the day of randomization (Baseline).

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

The eDiary assessments are performed throughout the study and are not confined to scheduled visits. Refer to Appendix A for frequency and duration of these assessments.

6.5.1 Screening Period

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

The screening period for all subjects is 3 weeks to allow for washout of any excluded therapies. Subjects will have a telephone contact approximately 2 weeks prior to the scheduled Baseline visit to review inclusion and exclusion criteria, check on any

procedure-related adverse events, and remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred with the medical monitor's agreement should more than 3 weeks be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition). Screening procedures may be repeated with the medical monitor's agreement.

The subject may be rescreened once with the medical monitor's agreement.

6.5.2 Screening Visit

The following screening procedures are to be performed at the Screening visit, preferably in the order shown below:

- Obtain written informed consent prior to any protocol-mandated procedures, including the stopping of any excluded therapies
- Collect demographic information (sex, date of birth, race, ethnicity)
- Ask subject to complete the WI-NRS scale on paper
- Register Screening visit into the IWRS
- Obtain ECG
- Obtain vital signs
- Review subject's medical history (including pruritus treatments in the past 3 months and current medications)
  - Record only significant/relevant medical history, to include the onset date of itch (as specifically as known)
  - Review for the presence of any underlying conditions that may exclude the subject from study eligibility
  - Female subjects should be queried regarding their childbearing potential and history of, or current, breast masses or abnormal discharge, and history of mammography (if applicable), and history of abnormal vaginal bleeding or discharge
- Perform complete physical examination (including height and weight)
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent who are not using hormonal contraception or other hormonal therapies at Screening

- Endocrine
- Hematology
- Chemistry
- Serology
- Serum IgE
- Iron studies
- Optional: additional assessments (refer to Section 6.2.3)

- Review subject's tentative eligibility according to the Inclusion/Exclusion criteria
  - The results of all screening evaluations, including laboratory and ECG results, must be reviewed for clinical significance by the PI or designee, and may require further evaluation, prior to randomization of the subject on Baseline visit
- Schedule the Baseline visit and all future study visits to ensure subject's availability and visit compliance with the protocol visit windows
- Provide eDiary with instructions
- Confirm next scheduled visit

6.5.3 Mid-Screening Telephone Contact

The Mid-Screening Telephone Contact occurs 15 days (- 3 days) prior to the Baseline visit. During this telephone contact the following procedures are to be performed:

- Assess and record any changes in medications since the Screening visit
- Review subject's tentative eligibility according to Inclusion/Exclusion criteria
- Assess AEs and record SAEs caused by protocol-mandated interventions
- Review eDiary for compliance, re-train subject as needed
- Confirm next scheduled visit

6.5.4 Baseline Visit

The Baseline visit occurs 3 weeks (+3 days) after the screening visit. Eligibility must be confirmed prior to randomization. At the Baseline visit, the following procedures and assessments are to be performed, preferably in the order shown below:

- Ask the subject to complete the WI-VAS, ESS, and sPGA questionnaires
- Assess and record any changes in the subject's concomitant medications

- Assess and record any changes in the subject's medical history
  - Female subjects should be queried regarding history of, or current, breast masses or abnormal discharge, and history of mammography (if applicable), and history of abnormal vaginal bleeding or discharge
- Assess AEs and record SAEs caused by protocol-mandated interventions
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential and confirm the subject has a negative urine pregnancy test result prior to randomization (with positive or equivocal results confirmed by a serum pregnancy test)
- Confirm subject's eligibility based on the inclusion/exclusion criteria (to include review of eDiary compliance for eligibility)
- Randomize subject in IWRS if eligibility confirmed
- Perform targeted physical examination, including weight
- Dispense 1 bottle of study drug; subjects will take loading dose of 3 tablets while on site
- Assess and record any post-dose AEs and SAEs
- Confirm next scheduled visit

6.5.5 Week 1 Telephone Contact Visit

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

- Assess and record any changes in the subject's concomitant medications
- Assess and record any AEs and SAEs
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit

6.5.6 Week 2 Visit

The Week 2 visit occurs 14 days (-3/+1 days) after the Baseline visit. At the Week 2 visit, the following procedures and assessments are to be performed:

- Ask the subject to complete the WI-VAS, ESS, sPGA, and PGIC questionnaires

- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Obtain vital signs
- Assess and record any AEs and SAEs
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Collect returned study drug
- Utilize IWRS to assign 1 new bottle of study drug
- Confirm next scheduled visit date

6.5.7 Week 4 Visit

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

- Ask the subject to complete the WI-VAS, ESS, sPGA, and PGIC questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform targeted physical examination, including weight
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign 1 new bottle of study drug

- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.8 Week 6 Visit

The Week 6 visit occurs 42 days (± 3 days) after the Baseline visit. At the Week 6 visit, the following procedures and assessments are to be performed:

- Ask the subject to complete the WI-VAS, ESS, sPGA, and PGIC questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Obtain vital signs
- Perform targeted physical examination, including weight
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign 2 new bottles of study drug
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.9 Week 8 Telephone Contact Visit

The Week 8 visit is a telephone visit that occurs 56 days (± 3 days) after the Baseline visit. At the Week 8 visit, the following procedures and assessments are to be performed:

- Assess and record any changes in the subject's concomitant medications
- Assess and record any AEs and SAEs
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit

6.5.10 Week 10 Visit

The Week 10 visit occurs 70 days (+ 3 days) after the Baseline visit. At the Week 10 visit, the following procedures and assessments are to be performed:

- Ask the subject to complete the WI-VAS, ESS, sPGA, and PGIC questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Assess and record any AEs and SAEs
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential and confirm the subject has a negative urine pregnancy test result prior to randomization (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent who are not using hormonal contraception or other hormonal therapies at Screening
  - Endocrine
  - Hematology
  - Chemistry
- Collect PK blood sample
- Perform targeted physical examination, including weight
- Review study drug compliance
- Collect returned study drug
- Review eDiary for compliance, re-train subject as needed
- Confirm next scheduled visit

6.5.11 Follow-up Visit

The required Follow-up visit occurs 35 days (+7 days) after the Week 10 visit or the last dose of study drug (for subjects who discontinue study drug early).

At the Follow-up visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS

- Ask the subject to complete the WI-VAS, ESS, sPGA, and PGIC questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent who are not using hormonal contraception or other hormonal therapies at Screening
  - Endocrine
  - Hematology
  - Chemistry
- Assess and record any AEs and SAEs
- Collect eDiary device, review eDiary for compliance

6.5.12 Early Termination From the Study

Early termination of a subject from the study may occur due to loss to follow-up, withdrawal of consent by the subject. In accordance with legal requirements and International Council on Harmonization (ICH) –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 provided, the reason (adverse event, study burden, lack of efficacy, other) a subject withdrew consent will be recorded in the electronic Case Report Form (eCRF). The PI or site staff must make every effort to contact subjects who are suspected of being lost to follow-up. Attempts to contact such subjects must be documented in the subject's source documents.

7 ASSESSMENT OF SAFETY

7.1 Definitions

7.1.1 Adverse Event

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

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

7.1.2 Serious Adverse Event

An AE is considered "serious" if it results in any of the following outcomes:

- Death
- Life-threatening AE (i.e. the subject was at immediate risk of death from the event as it occurred. An event that might have led to death if it had occurred with greater severity is not "life-threatening")
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/ birth defect
- Important medical event (i.e. an event that may not result in death, be life-threatening, or require hospitalization, but which may be considered serious by the investigator or Sponsor, as it may jeopardize the subject and may require medical/surgical intervention to prevent one of the outcomes listed above). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

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

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

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

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

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

7.1.4 Deaths

Any deaths that occur from the time of informed consent to the follow-up visit, regardless of attribution, must be reported within 24 hours of investigator’s awareness of the death. See Safety 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 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, unless permanently surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female.

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

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

1. Surgical sterilization (e.g., bilateral tubal occlusion or ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
2. Total (as opposed to periodic or cyclic) abstinence from heterosexual intercourse, only if planned for the entire duration of the study period and consistent with the preferred and usual lifestyle for the subject
3. Hormonal contraception associated with consistent inhibition of ovulation; these may include (but are not necessarily limited to) oral, intravaginal, implantable, injectable, or transdermal delivery methods
4. Intrauterine device/system
5. Exclusive (sole) monogamous intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner; the male partner must have received medical assessment of the surgical success

Progesterone-only oral contraceptives are excluded as a highly effective method of contraception, as they do not consistently inhibit ovulation. Male or female condoms with or without spermicide, and female caps, diaphragms, and sponges with spermicide, or combinations (double barrier) are also excluded as highly effective contraceptive methods.

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

7.1.6 Worsening of Pruritus

Pruritus should be recorded as an AE or SAE only if considered by the investigator to have worsened in severity beyond the subject's typical fluctuations.

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

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

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

All AEs entered into the eCRF will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 ("Common Terminology Criteria for Adverse Events (CTCAE)" 2017) to describe the maximum intensity of the adverse event.

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

Table 1 Adverse Event Grading

Grade	Severity	Alternate Description[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 instrumental 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) v5.0

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

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

7.2.4 Assessment of Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. Causality of an AE will be assessed by the investigator using the following terms:

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

7.3 Follow-up of Adverse Events and Serious Adverse Events

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

7.4 Reporting Serious Adverse Events to the Sponsor and Institutional Review Board 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 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 Safety Form Report Completion Instructions for safety reporting instructions.

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

7.6 Emergency Unblinding

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

8 STATISTICAL METHODS

Endpoints will be summarized with descriptive statistics by treatment group and visit/timepoint. For continuous variables, the following information will be presented: n (number of subjects), mean, standard deviation, median, minimum and maximum. For categorical variables counts and percentages will be used. Summary statistics for imputed efficacy data will be reported based upon imputed data.

Baseline for measures other than the eDiary daily measures will be the last recorded value prior to the start of treatment. For daily measures including the WI-NRS, baseline will be the average result measured over the week prior to treatment.

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

8.1 Decision Rule and Sample Size

This study will use a 5% one-sided alpha level.

The target sample size of 200 randomized and dosed subjects (100 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% one-alpha level. A sample size of two hundred subjects results in at least 90% power assuming a placebo Week 10 4-point responder rate of CCI% and serlopitant 4-point responder rate of CCI%.

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

8.2 Handling of Missing Data

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

If a subject fails to complete their eDiary for a week or more, the WI-NRS endpoints, including the primary endpoint, may be missing. In this case, the WI-NRS change from baseline value will be imputed. The 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. Any missing changes will be imputed to produce and them combined with the prior known value to produce a change from baseline result. For

example, a placebo subject with known results at Week 4 but missing at Week 6 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 average placebo change from Week 4 to 6 (i.e. the average placebo decrease from Week 4 to 6).

For the responder endpoints, the same imputation will be performed and the responder status determined based upon the change from baseline and the subject's disposition and rescue medication status (See Section 8.8).

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 population (FAP) and will include all randomized subjects who were dispensed study drug. 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 Prior and Concomitant Medications

Prior and concomitant medications will be coded by the World Health Organization Drug Dictionary to Anatomical Therapeutic Classification (ATC) and preferred drug name.

Prior therapies (including over-the-counter medications) used to treat pruritus within the prior 3 months will be reported. Prior medications will be summarized by ATC level and preferred drug name and listed.

Concomitant medications will be summarized by ATC level and preferred drug name and listed. Concomitant medication use will be quantified and analyzed.

8.7 Treatment Compliance and Extent of Exposure

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

8.8 Efficacy Analyses

All efficacy endpoints will be summarized within the FAP using descriptive statistics by time point and treatment.

8.8.1 WI-NRS

Subject record their WI-NRS measurements daily in an electronic diary. These daily measures are combined into weekly measures (Baseline, Weeks 2, 4, 6, 8, 10, Follow-up) by averaging the daily measurements. Change from baseline is the difference between baseline and the post baseline weeks. Missing data will be imputed as outlined in Section 8.2. From this change from baseline the binary responder status (responder / non-responder) is created. A subject is a 4-point responder if their change from baseline is ≤ -4 (i.e. a decrease of at least 4). A 3-point responder is similarly defined. Subjects who withdraw from the study due to a lack of efficacy or require rescue therapy for treatment of worsening pruritus within four weeks prior to the timepoint will be defined as non-responders regardless of their change from baseline.

The daily WI-NRS endpoint (change from baseline in daily WI-NRS scores through Week 2) is the change between the baseline WI-NRS (same baseline as the weekly measures) and the daily measures over the first two weeks.

8.8.2 Primary Efficacy

The WI-NRS 4-point responder rate at Week 10 (primary endpoint) will be summarized by treatment group. The difference in responder rates between treatment arms will be tested using a CMH test controlling for the 'as randomized' stratification factors. Conceptually the hypotheses being tested are:

$$H_0: P_{Placebo} \geq P_{serlopitant} \qquad H_a: P_{Placebo} < P_{serlopitant}$$

where $P_{Placebo}$ is the percent of placebo responders and $P_{serlopitant}$ is the similar percent for serlopitant.

Sensitivity analyses using other missing data rules will be performed.

8.8.3 Secondary Efficacy and Exploratory

Secondary endpoints will be summarized with descriptive statistics by time point and treatment. These summary measures will include baseline, result at the time point and change from baseline as is appropriate for the endpoint. Missing data imputation will be limited to the WI-NRS and WI-VAS endpoints.

The differences between treatment groups for the WI-NRS 4-point at Weeks 2, 4, 6, and 8, and 3-point responder rates at Weeks 2, 4, 6, 8, and 10 will be tested using the CMH test identical to the one used for the primary endpoint.

The change from baseline to Weeks 2, 4, 6, 8, and 10 and Days 1–14 for the WI-NRS will be testing using an analysis of variance (ANOVA) model with treatment group and stratification factor as fixed effects. The change in WI-VAS to Weeks 2, 4, 6, and 10 will be tested using a similar ANOVA model.

8.9 Safety Analyses

8.9.1 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.

8.9.2 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.

8.9.3 Vital Signs

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

8.9.4 Electrocardiograms

The overall ECG assessment (abnormal or normal) will be summarized and descriptively characterized, along with a summary of how many subjects developed a post treatment abnormal result.

8.9.5 Physical Exams

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

8.10 Population Pharmacokinetics Analysis

The plasma concentrations of serlopitant and metabolites will be combined with the data from other serlopitant clinical studies for population PK analysis with PK endpoint of individual model parameter estimates and covariates identification. A specific population PK data analysis plan will be developed that will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques. The population PK analysis report will not be a part of the clinical study report for MTI-117.

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. The study may be terminated at the request of the US Food and Drug Administration, or if the approval to manufacture or to import study drug is revoked by those with jurisdiction. 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 may 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 will be assured that they may withdraw from the study at any time without jeopardizing medical care related to or required as a result of study participation. The original signed consent form will be maintained in the investigator site file. Copies of signed consent forms will be provided to the subject.

9.6 Communication with the Institutional Review Board 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, ICF, 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 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, IWRS, eDiary, and ECG data will be recorded in an eCRF system (note: collection of central laboratory and PK blood draws will be recorded in the eCRF). 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 or EC within 90 days from the end of the clinical study. The end of the clinical study is defined as the last study visit for the last subject.

9.11 Publication of Results

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

9.12 Final Report

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

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APPENDIX A SCHEDULE OF ACTIVITIES AND ASSESSMENTS

Table 2 Schedule of Visit Activities

Examination	Screening	Mid-Screening[TC] (-3 days)	Baseline[1] (+3 days)	Week 1[TC] (± 3 days)	Week 2 (-3 /+1 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 8[TC] (± 3 days)	Week 10 (+ 3 days)	F/U[2]
Demographics	X									
Informed consent	X									
Paper WI-NRS[3]	X									
WI-VAS			X		X	X	X		X	X
ESS			X		X	X	X		X	X
sPGA			X		X	X	X		X	X
PGIC					X	X	X		X	X
ECG	X					X				X
Vital signs	X		X		X	X	X		X	X
Medical history (and prior medications)	X	X	X							
Physical exam[4]	X		X			X	X		X	X
Concomitant medications			X	X	X	X	X	X	X	X
Labs[5]	X					X			X	X
Urine pregnancy test[6]	X		X			X			X	X
PK blood draw									X	
Review of I/E criteria	X	X	X							
Dispense/collect eDiary	X									X
eDiary review/compliance[7]		X	X	X	X	X	X	X	X	X
Dispense and/or collect study drug			X		X	X	X		X	
Review study drug compliance				X	X	X	X	X	X	
AEs/SAEs[8]	X	X	X	X	X	X	X	X	X	X

[TC]Telephone Contact: The Mid-Screening telephone contact should occur at least 15 days prior to the scheduled Baseline visit.

[1]All visits and windows should be scheduled based on the Baseline Visit (Day 1)

[2]The Follow-up (F/U) visit occurs 35 days (+ 7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early.

[3]WI-NRS at Screening visit will be collected manually on paper for Inclusion/Exclusion criteria. All subsequent WI-NRS are collected daily via eDiary.

[4]Screening physical exam is complete and includes height and weight; other physical exams are targeted and include weight.

[5]Labs are ideally performed in the morning, particularly at visits with endocrine assessments (including Reproductive Endocrinology for females under 55 at age of consent who are not using hormonal contraception or other hormonal therapies at Screening) at Screening, Week 10, and Follow Up).

[6]Female subjects of childbearing potential only. Serum pregnancy test is required for positive or equivocal results.

[7]See Table 3 for eDiary assessments

[8]During the period between informed consent and first study drug dose, only SAEs caused by a protocol-mandated intervention will be collected.

Table 3 Schedule of eDiary Assessments

An eDiary device is provided to subjects at the Screening visit and collected at the Follow-up visit.

Device	Assessment	Frequency and Duration of Assessment
eDiary	WI-NRS	Once daily from Screening visit through the Follow-up visit
eDiary	Dosing	Once daily from Baseline visit through Week 10 visit or study drug discontinuation

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

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

Note: This Appendix may be replaced if applicable (e.g., if updated by the FDA) through site communications without requiring a protocol amendment.

1. boceprevir
2. clarithromycin
3. cobicistat
4. conivaptan
5. danoprevir and ritonavir
6. diltiazem
7. elvitegravir and ritonavir
8. idelalisib
9. indinavir and ritonavir
10. itraconazole[a]
11. ketoconazole[a]
12. lopinavir and ritonavir
13. nefazodone
14. nelfinavir
15. paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
16. posaconazole[a]
17. ritonavir
18. saquinavir and ritonavir
19. telaprevir
20. tipranavir and ritonavir
21. troleandomycin
22. voriconazole[a]
23. regular grapefruit juice consumption (note: The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Grapefruit juice may be a strong or a moderate CYP3A inhibitor depending on the preparation)[b]

[a] When administered topically, it may not be considered a strong CYP3A4 inhibitor due to limited systemic absorption.

[b] The occasional consumption of grapefruit juice or the consumption of grapefruit or other citrus fruits (e.g., pomelo, lemon, lime, Seville orange, bitter orange, starfruit) is not contraindicated.

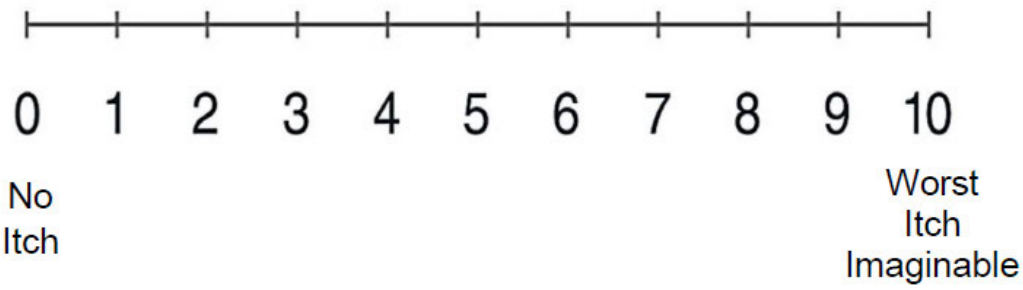
APPENDIX C WORST ITCH NUMERIC RATING SCALE QUESTIONNAIRE

NRS for Itch Intensity

For the following item, please provide the response that best describes your itching on the Numeric Rating Scale where 0 = No itch and 10 = Worst itch imaginable

CIRCLE THE NUMBER ON THE SCALE THAT CORRESPONDS WITH YOUR INTENSITY LEVEL

How would you rate your WORST itch in the past 24 hours, on a scale from 0 to 10, where 0 is No itch and 10 is Worst itch imaginable?



APPENDIX D EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public place (e.g., a theater or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car or bus, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

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