- **Protocol number:** MTI-107
- **Document title:** An open-label long-term safety study of serlopitant for the treatment of pruritus.
- **Version numbers:** Protocol Version 3.0
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CLINICAL STUDY PROTOCOL

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
ClinicalTrials.gov ID:	TBD
Protocol No.:	MTI-107
Protocol Version/Date:	FINAL 1.0 18 December 2017
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063

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 Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

_____
Principal/Coordinating Investigator's printed name

_____ _____
Principal/Coordinating Investigator's signature Date (DD-MMM-YYYY)

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

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Approved by:

PPD

PPD

PROTOCOL SYNOPSIS

Study Title:	An Open-Label Long-Term Safety Study of Serlopitant for the Treatment of Pruritus
Protocol Number:	MTI-107
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Primary objective: • To assess the long-term safety of serlopitant in adults with pruritus associated with prurigo nodularis (PN), atopic dermatitis (AD), or psoriasis. Secondary objectives: • To assess change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS). • To assess change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN. • To assess whether serlopitant produces physical dependence.
Study Design:	Study MTI-107 is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. The study will consist of two periods, for a total study period of approximately 56 weeks: • Treatment period: 52 weeks • Post-drug observation period: 4 weeks During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Standard therapy for the concurrent skin lesions and pruritus may be employed during this study. After completion of the 52-week treatment period, all subjects will enter a 4-week post-drug observation period. Subjects who discontinue treatment early will have a post-drug observation visit 4 weeks after their last dose of serlopitant.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 400 subjects
Study Population:	The study will enroll adults with pruritus due to PN, AD, or psoriasis. Inclusion Criteria (Subjects must meet the following criteria to be enrolled into the study): 1. Male or female, age 18 years or older at consent. 2. Subject reports pruritus in the 24-hour period prior to enrollment and: a. Has completed a prior applicable clinical study of serlopitant without a serious adverse event (SAE) that was assessed as likely related to the study drug

	OR b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and Sponsor has approved enrollment. 3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year) from the time of the Baseline visit until 2 weeks after last dose of study drug. 4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies). 2. Presence of a psychiatric diagnosis (such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol abuse disorder) meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria in past 3 years, history of suicidal ideation within the past 3 years or any history of suicide attempt. 3. Presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject. 4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107. 5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment. 6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment. 7. Currently pregnant or breastfeeding or planning to become pregnant during the study.
Study Drug:	Serlopitant 5 mg tablets
Dosage:	Serlopitant: 5 mg once daily orally for 52 weeks
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) and 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 • Assessment of physical dependence following chronic study drug exposure, in the monitored 4-week post-drug discontinuation period
Efficacy Endpoints:	• Changes from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52 • Changes from baseline in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PROMIS-PIQ) score for Itch (General, Scratching Behavior, Mood and Sleep, Activity and Clothing) to Weeks 20, 36, and 52 • Changes from baseline in Dermatology Life Quality Index (DLQI) (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52

	• Changes from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52
Statistical Methods:	All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population. Data will be summarized with descriptive statistics by visit. For continuous variables, the following information will be presented: n, mean, standard deviation, median, minimum and maximum. For categorical variables, counts and percentages will be used. All adverse events (AEs) will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by specified time periods in order to understand the evolution of TEAEs over time. Additionally, the pre-specified TEAEs and SAEs that may be associated with physical dependence will be summarized separately. An overview of AEs, which includes subject incidence of TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Summary statistics for actual safety laboratory values and for changes from baseline will be tabulated 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. A listing of all out-of-range laboratory test results, including assessment of clinical significance will also be provided. The observed vital sign data and change from baseline will be summarized with descriptive statistics and presented in a listing. The overall ECG assessment (abnormal or normal) and parameters will be summarized along with a summary of how many subjects developed a post-treatment abnormal result and will be presented in a listing. Physical exam findings will be recorded by the sites within medical history or AEs and otherwise not summarized, with the exception of weight, and change from baseline in weight. The WI-NRS, PROMIS-PIQ, DLQI, and IGA PN-S, will be summarized with descriptive statistics by visit.
Study Sites:	Approximately 120 study sites
Expected Duration of Subject's Participation	Approximately 56 weeks: 52 weeks of treatment, and a post-drug observation period of 4 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CYP3A4	cytochrome-P 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
FSH	Follicle-stimulating hormone
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor
NRS	Numeric rating scale
PI	Principal Investigator
PK	Pharmacokinetics
PROMIS-PIQ	Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ)
PN	Prurigo nodularis
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus

Pruritus, or itch, is defined as an unpleasant sensation that evokes a desire to scratch (Ikoma 2006). Itch and pain, although closely related, are distinct sensations: itch elicits a scratching response, whereas pain causes a withdrawal response.

Emerging research in neurobiology has greatly expanded the understanding of pruritus signaling. Pruritoceptors (itch-sensory nerve fibers) consist of two distinct classes of nerve fibers: histamine-responsive mechanoinsensitive C-fibers, and histamine-unresponsive mechanosensitive polymodal C and Aδ fibers that are activated by cowhage (highly pruritic spicules from the pods of the cowhage plant *Mucuna pruriens*) (Schmelz 2015). The second class of histamine-unresponsive, cowhage-responsive nerve fibers has been of particular interest in pruritus research, as C-fibers that have a strong and sustained response to histamine comprise only about 20% of the overall mechanoinsensitive C-fiber population (Steinhoff 2006), and a significant proportion of chronic pruritic conditions do not appear to involve histamine-mediated pruritus signaling (Ikoma 2006). Substance P (SP) is a prominent pruritogen (itch mediator) in this histamine-independent pruritus pathway (Chuquilin 2016).

Pruritus stimuli in the skin are transmitted via sensory neurons that have their cell bodies in the dorsal root ganglia (DRG) and are linked to second-order neurons in the spine (Carstens 2016, Luo 2015). Following activation of these DRG sensory neurons, the pruritus signal is transmitted to the second-order spinal neurons primarily by SP, gastrin-releasing peptide, and glutamate in histamine-independent pruritus, and primarily by glutamate in histamine-mediated pruritus (Chuquilin 2016).

Spinal itch neuron projections ascend via the contralateral spinothalamic tract to the thalamus and via the lateral spinoparabrachial tract to the lateral parabrachial nucleus, from which point they activate multiple centers in the somatosensory cortex, the premotor cortex, and the cingulate cortex – areas involved in the sensory processing and motor response (scratching) to the itch signal (Carstens 2016, Chuquilin 2016).

1.1.1 Role of Substance P and the Neurokinin-1 Receptor in Pruritus

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 (NK_1-R), neurokinin-2, and neurokinin-3 receptors (Harrison 2001). The neurokinin-1 receptor, in particular, has been studied in great detail. NK_1-R is the primary receptor for SP in the human body, and is found on multiple cell types, including central and peripheral neurons, keratinocytes, mast cells, and dendritic cells (El-Nour 2006, Ständer 2015).

NK_1-R 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-R 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).

1.2 Serlopitant

1.2.1 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 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.

1.2.2 Serlopitant Clinical Summary

In humans, serlopitant has been administered to over 1000 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 males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young and elderly subjects. A single loading dose of up to 15 mg followed by 6 to 8 weeks of up to 5 mg daily doses has been well tolerated in adults with chronic pruritus and prurigo nodularis (PN).

Pharmacokinetic data demonstrate good plasma exposures with oral dosing, linear dose-dependent increases in plasma concentration and systemic exposure, a plasma t1/2 appropriate for 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 CCI, M2/M2a CCI, and M3 CCI. 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.

1.2.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

TCP-101 was a double-blind, placebo-controlled, multi-center study that compared serlopitant 0.25 mg, 1 mg, or 5 mg vs. placebo for the treatment of chronic pruritus. A total of 257 adult subjects 18-65 years of age with chronic pruritus were randomized to receive one of the four dose groups in a 1:1:1:1 randomization. Subjects received a loading dose of 3 tablets on Day 1 and thereafter received 1 tablet per day for 6 weeks. The primary efficacy endpoint was itch severity as measured on a Visual Analog Scale (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 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 of the percentage of subjects who were 4-point responders on average VAS at Week 8, 25.0% of placebo subjects and 54.4% of serlopitant subjects were 4-point responders.

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

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

The results of the Phase 2 studies in PN and 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 pruritus in subjects with PN (in concurrent Phase 3 studies MTI-105 and MTI-106), atopic dermatitis (AD) (in ongoing Phase 2 study MTI-103), and psoriasis (in ongoing Phase 2 study MTI-109).

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

2 STUDY OBJECTIVES

The primary objective of this study is to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis.

The secondary objectives of this study are to assess the change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS); to assess the change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN; and to assess whether serlopitant produces physical dependence.

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. Approximately 120 study sites may enroll subjects in this long-term safety study.

This study will consist of two periods, for a total study period of approximately 56 weeks:

- Treatment period: 52 weeks
- Post-drug observation period: 4 weeks

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally (Section 5.3).

Standard therapy for the concurrent skin lesions and pruritus may be employed during this study (Section 5.7.1).

The WI-NRS during a 24-hour recall period will be assessed by the subject at each study visit.

For those subjects with PN, the severity and extent of PN will be assessed at selected visits, using the IGA-PN-S, and photographs of representative areas with PN will be taken at selected visits at a subset of sites.

The Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PROMIS-PIQ) and the Dermatology Life Quality Index (DLQI) will be administered at selected visits.

After completion of the 52-week treatment period, all subjects will enter a 4-week post-drug observation period. Subjects who discontinue treatment early will have a post-drug observation visit 4 weeks after their last dose of serlopitant. During this monitored discontinuation period, solicited safety evaluations will assess the potential for serlopitant to produce physical dependence.

3.2 Rationale for Study Design and Dose Selection

The current MTI-107 study is designed to confirm the long-term safety of serlopitant for the treatment of pruritus in patients with PN, AD, and psoriasis. The 5 mg dose of serlopitant was selected for this study based on the favorable efficacy, safety, and tolerability profile of serlopitant at this dose level in completed studies.

3.3 Study Endpoints

3.3.1 Safety Endpoints

The 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
- Assessment of physical dependence following chronic study drug exposure, in the 4-week post-drug discontinuation period.

3.3.2 Efficacy Endpoints

The efficacy endpoints are as follows:

- Changes from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Changes from baseline in PROMIS-PIQ score for Itch (General, Scratching Behavior, Mood and Sleep, Activity and Clothing) to Weeks 20, 36, and 52

- Changes from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Changes from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52

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 safety data on a regular basis throughout the study.

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 400 adult subjects with pruritus due to PN, AD, or psoriasis will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. Subject reports pruritus in the 24-hour period prior to enrollment and:
   a. Has completed a prior applicable clinical study of serlopitant without an SAE that was assessed as likely related to the study drug

      OR

   b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and Sponsor has approved enrollment.
3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year, refer to section 7.1.5 for acceptable methods of contraception) from the time of the Baseline visit until 2 weeks after last dose of study drug.
4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies).
2. Presence of a psychiatric diagnosis (such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol abuse disorder) meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria in past 3 years, history of suicidal ideation within the past 3 years or any history of suicide attempt.
3. Presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject.
4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107.
5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment.
6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment (Appendix B).
7. Currently pregnant or breastfeeding or planning to become pregnant during the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

The study drug in this study is serlopitant 5 mg 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 study drug will be provided in bottles that can be stored at room temperature (59-86°F, 15-30°C).

Each bottle will each contain 18 serlopitant tablets.

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

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Subjects will be instructed to take all doses from Baseline Visit (Study Day 1) until the Week 52 Visit, once a day and not within 2 hours before or after a meal.

Should the study drug be withheld (without intent to discontinue study drug, Section 5.6), the drug may be resumed at the discretion of the investigator, at the same dosing regimen.

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

Each dose of study drug after the first dose must be administered once daily, and not within 2 hours before or after a meal. If a dose is missed, that dose will be considered and documented as a missed dose. Dosing should resume as directed the next day.

5.6 Study Drug Discontinuation

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

- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion
- Baseline serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) (exception may be made for retesting within 28 days of enrollment as approved by the Medical Monitor)
- A female subject becomes pregnant
- The subject decides to discontinue study drug, or withdraws consent from the study
- The subject reports use of a strong CYP3A4 inhibitor (as listed in Appendix B) within 4 weeks of the study visit at which it was reported, initiates any investigational medication, or other NK_1-R antagonist (exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)

- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion

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

Subjects who discontinue study drug prior to completing the treatment period will enter a 4-week follow-up period following the last dose of study drug (Section 6.4.10). Every effort should be made for subjects to complete this follow-up visit after a subject has discontinued from study drug.

5.7 Concomitant and Excluded Therapies

Concomitant therapies include any therapies (including over-the-counter medications) used by a subject from initiation of study drug 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 and routine preventative immunizations.

5.7.1 Excluded Therapies

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

- NK_1-R antagonists (other than study drug, exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)
- Strong CYP3A4 inhibitors (See Appendix B; exceptions may be made for use within 4 weeks of the study visit at which it was reported)
- Any investigational drug therapy other than serlopitant

Use of any excluded therapies should be reported as soon as possible, and will be recorded as protocol deviations for subjects who receive them. Subjects may be discontinued from the study drug (Section 5.6).

5.8 Assignment to Treatment

Eligible subjects will receive serlopitant 5 mg tablets.

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. Missed doses will be recorded as reported by the subject. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

6 STUDY SCHEDULE AND ASSESSMENTS

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

The Itch NRS is a validated, self-reported instrument for measurement of itch intensity. WI-NRS scores will be captured as per Appendix A. Subjects are asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicate greater itch intensity. In this study, WI-NRS during a 24-hour recall period prior to the specified visit will be captured.

6.1.2 Investigator's Global Assessment of PN Stage

The IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA PN-S uses clinical characteristics including the number of nodules and their thickness, as guidelines for the overall severity assessment. IGA PN-S scores will be captured as per Appendix A. Each assessment during the study must be done by the principal investigator (PI) or designee. Every effort should be made to ensure that all assessments for a given subject are done by the same individual throughout the study. However, a change in assessor for a given subject, though not ideal, will not be considered a protocol deviation.

6.1.3 Patient-Reported Outcomes Measurement Information System Itch Questionnaire

PROMIS-PIQ is an itch-specific instrument that measures quality of life impairment related to itch in the previous week. The PROMIS-PIQ includes 4 domains (General, Scratching Behavior, Mood and Sleep, and Activity and Clothing). Subjects will complete the PROMIS-PIQ short forms as per Appendix A.

6.1.4 Dermatology Life Quality Index

DLQI is a dermatology specific quality of life instrument designed to assess the impact of the skin disease on a subject's quality of life over the prior week. It is a ten-item questionnaire that assesses overall quality of life (QOL) and six aspects that may affect QOL (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment). The DLQI questionnaire will be collected as per Appendix A.

6.1.5 Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as per Appendix A. These areas may include the extensor surfaces of both arms and both legs (overview of both legs, detail of lower legs), and the abdomen and back. The central photography vendor will provide photographic equipment to the sites for use during the study. Detailed instructions will be provided in a Photography Manual.

6.2 Safety Parameters

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

6.2.1 Vital Signs

Vital signs will include measurements of heart rate, 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 as per Appendix A and at unscheduled study visits when clinically indicated. When possible, assessment of vital signs should precede blood draw.

6.2.2 Physical Examination

Physical examinations will be performed as per Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the Baseline visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. The subjects' height and weight will be measured as per Appendix A.

6.2.3 Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected as per Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified. When possible, blood draws should follow ECGs and vital sign measurements if they occur on the same visit.

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

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, uric acid, total protein, alanine

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel

- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)

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. When possible, ECGs should precede measurement of vital signs and blood draw for clinical laboratory tests. ECGs will be performed as per Appendix A and at unscheduled study visits when clinically indicated. ECGs will be reviewed and reported by a central ECG vendor. The ECG machine and detailed instructions will be provided by the ECG vendor.

6.2.5 Assessment of Potential for Physical Dependence

NK_1-R antagonist dependence has not previously been described and therefore a drug class-specific, reliable and sensitive instrument for the assessment of withdrawal symptoms has not been developed. A surrogate assessment tool, such as those developed for opioid or benzodiazepine dependence, is not available.

In the statistical analysis plan (SAP), the Sponsor will specify a targeted medical event list (TEAEs) that may be associated with physical dependence, and evaluate reports of these events in the monitored 4-week post-drug discontinuation period.

6.3 Subject Flow Diagram

The visit schedule and assessments are summarized in Appendix A.

6.4 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 and 6.2. The timing of each study visit is relative to the day of enrollment (Baseline Visit).

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

6.4.1 Baseline Visit

The Baseline Visit may coincide with the final visit of the MTI-103, MTI-105, MTI-106, or MTI-109 studies.

The following procedures are to be performed at the Baseline Visit (Day 1):

- Obtain written informed consent prior to any protocol-mandated procedures (must be obtained prior to any other assessments)
- Confirm subject's eligibility based on the inclusion/exclusion
- Collect demographic information (when permitted by regional laws or guidelines: sex, date of birth, race/ethnicity)
- Collect any concomitant medications
- Review and record subject's medical history, including ongoing TEAEs from prior study (if applicable)
- Perform complete physical examination (including height and weight)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (exception: participants in MTI-103, MTI-105, MTI-106, and MTI-109 who have had these labs in prior 14 days, in the context of that study)
  - Hematology
  - Chemistry
  - Reproductive endocrine labs for females under 55 years of age at consent
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Register Baseline Visit into the Interactive Web Response System (IWRS)
- Dispense study drug
- Confirm next scheduled visit date

6.4.2 Week 4 Visit

The Week 4 Visit occurs 28 days (±7 days) after the Baseline Visit. At the Week 4 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.3 Week 8 Visit

The Week 8 Visit occurs 56 days (±7 days) after the Baseline Visit. At the Week 8 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)

- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.4 Week 12 Visit

The Week 12 Visit occurs 84 days (±7 days) after the Baseline Visit. At the Week 12 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.5 Week 20 Visit

The Week 20 Visit occurs 140 days (±7 days) after the Baseline Visit. At the Week 20 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.6 Week 28 Visit

The Week 28 Visit occurs 196 days (±7 days) after the Baseline Visit. At the Week 28 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Hematology
  - Chemistry

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.7 Week 36 Visit

The Week 36 Visit occurs 252 days (±7 days) after the Baseline Visit. At the Week 36 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.8 Week 44 Visit

The Week 44 Visit occurs 308 days (±7 days) after the Baseline Visit. At the Week 44 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.9 Week 52 Visit

The Week 52 Visit occurs 364 days (±7 days) after the Baseline Visit. At the Week 52 Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Hematology
  - Chemistry

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Confirm next scheduled visit date

6.4.10 Early Treatment Discontinuation Visit/Post-Drug Observation

The Early Treatment Discontinuation (ETD) Visit occurs within 28 days of last dose for subjects who discontinue serlopitant treatment prior to Week 52.

The Post-Drug Observation Visit occurs 28 days (±7 days) after the Week 52 Visit.

At the ETD/Post-Drug Observation Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination with weight
- Obtain ECG (ETD only)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Ask subject to complete WI-NRS

- Ask the subject to complete the following questionnaires (ETD only):
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography, ETD only)
- Collect returned study drug (ETD only)

6.4.11 Early Termination

Early termination of a subject from the study may occur due to loss to follow-up or withdrawal of consent by the subject. In accordance with legal requirements and International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If 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). Attempts to contact subjects who are suspected of being lost to follow-up 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 not considered SAEs: a visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event), an elective surgery planned prior to signing consent, admission as per protocol for planned medical/surgical procedure, and/or routine health assessments requiring admission for baseline/trending of health status (e.g. routine colonoscopy).

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

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

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

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

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

If the clinically significant laboratory, vital sign, or ECG abnormality is a sign associated with a confirmed disease or condition (e.g. elevated creatinine in a subject diagnosed with

chronic kidney disease), only the diagnosis (chronic kidney disease) needs to be recorded on the AE eCRF (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; a post-menopausal 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
3. Hormonal contraception associated with consistent inhibition of ovulation; these may include (but are not necessarily limited to) oral, intravaginal, implantable, injectable, or transdermal delivery methods.
    a. Progesterone only oral contraceptives are excluded as a highly effective method, as they do not consistently inhibit ovulation.
4. Intrauterine device/system
5. Exclusive monogamous intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner

Any pregnancy occurring in a female subject or the female partner of a male subject, from the first study drug administration through the 4-week 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 or Underlying Pruritic Skin Disease

Pruritus or the underlying pruritic skin disease (PN, AD, or psoriasis) 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. It is important to include a description of the nature of the unexpected worsening when recording the AE or SAE (e.g. new PN lesions in previously uninvolved skin).

7.2 Methods and Timing for Recording and Reporting Adverse Events

7.2.1 Adverse Event Reporting Period

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

AEs and SAEs will be recorded from the first study drug administration through the follow-up visit. After the 4-week follow-up visit, only SAEs that are believed to be drug-related should be reported.

After informed consent, 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 Baseline visit procedures but are not enrolled into the study will not have SAEs recorded in the clinical database.

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

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

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

Table 1 Adverse Event Grading

Grade	Severity	Alternate Description[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) v4.03

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 treatment with study drug or participation in the study is not the cause of the AE or SAE.

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

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

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

Please see the 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 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.

8 STATISTICAL METHODS

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

Baseline will be the last recorded value prior to the start of treatment.

A SAP describing all statistical analyses will be written as a separate document.

8.1 Handling of Missing Data and Excluded Therapy Use

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

8.2 Analysis Population

All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population.

8.3 Subject Disposition

An accounting of all 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.

8.4 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.5 Concomitant Medications

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

8.6 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.

8.7 Efficacy Analyses

Descriptive statistics will be used to summarize the following:

- Changes from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Changes from baseline in PROMIS-PIQ score for Itch (General, Scratching Behavior, Mood and Sleep, Activity and Clothing) to Weeks 20, 36, and 52
- Changes from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Changes from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52.

Data will be summarized by time point using frequency tabulations or descriptive statistics as appropriate. Observed results, as well as change from baseline will be summarized, as appropriate.

8.8 Safety Analyses

8.8.1 Adverse Events

All AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by time period in order to understand the evolution of TEAEs over time. Thus, in addition to the TEAE analysis over the entire 12-month treatment time, results will be presented for the following periods: 0 to 4 weeks, > 4 to 12 weeks, > 12 to 28 weeks, > 28 weeks to 36 weeks, > 36 to end of treatment, and end of treatment to end of the study. Additionally, the pre-specified TEAEs and SAEs that may be associated with physical dependence will be summarized separately. For incidence reporting, if a subject reported more than one TEAE 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, TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, end date (if ended), seriousness, severity, action taken regarding the study drug, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided.

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

8.8.2 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, and listings will be provided.

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. A listing of all out-of-range laboratory test results, including assessment of clinical significance, will also be provided.

8.8.3 Vital Signs

The observed vital sign data and change from baseline for each scheduled visit will be summarized with descriptive statistics, and presented in a listing.

8.8.4 Electrocardiograms

The overall ECG assessment (abnormal or normal) and parameters will be summarized along with a summary of how many subjects developed a post-treatment abnormal result, and will be presented in a listing.

8.8.5 Physical Exams

Physical exam findings will be recorded by the sites within medical history or adverse events and otherwise not summarized, with the exception of weight and change from baseline in weight.

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. A written statement fully documenting the reasons for study termination will be provided to the IRB or EC.

9.3 Monitoring and Auditing Procedures

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

9.4 Transfer of Obligations

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

9.5 Informed Consent

The purpose of the study, the procedures to be carried out, and any potential risks of study participation will be described in non-technical terms in the ICF. After having reviewed and understood the ICF, subjects will be required to read, sign, and date an IRB-approved or EC-approved consent form before any study-specific procedures are carried out. Subjects 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(R2) 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, Investigator Brochure, 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 and ECG data will be recorded in an eCRF system. Data will be entered at the site by the appropriately designated and trained site personnel. All source documents from which eCRF entries are derived should be placed in the subject's medical records. eCRFs will be completed for every subject screened in the study. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

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(R2) guideline and the site's data retention policies. These records must be available for inspection by the Sponsor, monitor, and regulatory authorities. Furthermore, the investigators/institutions will permit trial-related monitoring, audits, EC review, and inspections by a competent authority as necessary and provide direct access to source data/documents.

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

9.9 Good Clinical Practice and Ethical Study Conduct

The study procedures outlined in this protocol will be conducted in accordance with applicable ICH Guidelines, including ICH E6(R2): Good Clinical Practice. 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

Examination	Baseline[1]	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 20 (±7 days)	Week 28 (±7 days)	Week 36 (±7 days)	Week 44 (±7 days)	Week 52 (±7 days)	Early Treatment Discontinuation	Post-drug observation[2]
Informed consent	X										
I/E criteria	X										
Demographics/ Medical History	X										
Physical exam[3]	X[4]	X	X	X	X	X	X	X	X	X[4]	X[4]
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Labs[5]	X[1]	X		X		X			X	X	X
Urine pregnancy test[6]	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X		X		X	X	
WI-NRS	X	X	X	X	X	X	X	X	X	X	X
IGA PN-S (PN subjects only)	X	X	X	X	X	X	X	X	X	X	X
PROMIS-PIQ and DLQI	X				X		X		X	X	
Photographs (if applicable)	X				X		X		X	X	
Dispense and/or collect serlopitant	X	X	X	X	X	X	X	X	X	X	
Review study drug compliance		X	X	X	X	X	X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X

1 Baseline may coincide with the final visit of prior applicable study; Baseline labs do not need to be repeated if completed within prior 14 days

2 The post-drug observation visit occurs 28 days (± 7 days) after the Week 52 visit

3 Baseline physical exam is complete; all other physical exams are targeted

4 Height/weight at Baseline and weight at ETD/post-drug

5 Hematology and Chemistry at Baseline, Weeks 4, 12, 28, 52 and ETD/post/drug; Reproductive Endocrinology at Baseline, Weeks 28 and 52 (females under 55 years of age at consent)

6 For females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

The list of strong CYP3A4 inhibitors is based on the United States Food and Drug Adminstration (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. regular grapefruit juice consumption
9. idelalisib
10. indinavir and ritonavir
11. itraconazole[a]
12. ketoconazole[a]
13. lopinavir and ritonavir
14. nefazodone
15. nelfinavir
16. paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
17. posaconazole[a]
18. ritonavir
19. saquinavir and ritonavir
20. telaprevir
21. tipranavir and ritonavir
22. troleandomycin
23. voriconazole[a]

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

CLINICAL STUDY PROTOCOL

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
ClinicalTrials.gov ID:	TBD
Protocol No.:	MTI-107
Protocol Version/Date:	Version 1.1/11 April 2018
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063

Confidentiality Statement:

SIGNATURE PAGE FOR INVESTIGATOR(S)

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
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Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063

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

_____
Principal/Coordinating Investigator's printed name

_____ _____
Principal/Coordinating Investigator's signature Date (DD-MMM-YYYY)

SIGNATURE PAGE FOR COORDINATING INVESTIGATOR

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
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I have read the protocol and agree to conduct this study in accordance with the protocol, all relevant laws and regulations in force at the time, International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

PPD

PPD

13Apr2018
Date (DD-MMM-YYYY)

PPD

Country of Coordinating Investigator

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
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Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063

Approved by:

PPD

Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Study Title:	An Open-Label Long-Term Safety Study of Serlopitant for the Treatment of Pruritus
Protocol Number:	MTI-107
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Primary objective: • To assess the long-term safety of serlopitant in adults with pruritus associated with prurigo nodularis (PN), atopic dermatitis (AD), or psoriasis. Secondary objectives: • To assess change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS). • To assess change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN. • To assess whether serlopitant produces physical dependence.
Study Design:	Study MTI-107 is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. The study will consist of two periods, for a total study period of approximately 56 weeks: • Treatment period: 52 weeks • Post-drug observation period: 4 weeks During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Standard therapy for the concurrent skin lesions and pruritus may be employed during this study. After completion of the 52-week treatment period, all subjects will enter a 4-week post-drug observation period. Subjects who discontinue treatment early will have a post-drug observation visit 4 weeks after their last dose of serlopitant.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 400 subjects
Study Population:	The study will enroll adults with pruritus due to PN, AD, or psoriasis. Inclusion Criteria (Subjects must meet the following criteria to be enrolled into the study): 1. Male or female, age 18 years or older at consent. 2. Subject reports pruritus in the 24-hour period prior to enrollment and: a. Has completed a prior applicable clinical study of serlopitant without a serious adverse event (SAE) that was assessed as likely related to the study drug

	OR b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and Sponsor has approved enrollment. 3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year) from the time of the Baseline visit until 2 weeks after last dose of study drug. 4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies). 2. Presence of a psychiatric diagnosis (such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol abuse disorder) meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria in past 3 years, history of suicidal ideation within the past 3 years or any history of suicide attempt. 3. Presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject. 4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107. 5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment. 6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment. 7. Currently pregnant or breastfeeding or planning to become pregnant during the study.
Study Drug:	Serlopitant 5 mg tablets
Dosage:	Serlopitant: 5 mg once daily orally for 52 weeks
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) and 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 • Assessment of physical dependence following chronic study drug exposure, in the monitored 4-week post-drug discontinuation period
Efficacy Endpoints:	• Changes from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52 • Changes from baseline in Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PROMIS-PIQ) score for Itch (General, Scratching Behavior, Mood and Sleep, Activity and Clothing) to Weeks 20, 36, and 52 • Changes from baseline in Dermatology Life Quality Index (DLQI) (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52

	• Changes from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52
Statistical Methods:	All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population. Data will be summarized with descriptive statistics by visit. For continuous variables, the following information will be presented: n, mean, standard deviation, median, minimum and maximum. For categorical variables, counts and percentages will be used. All adverse events (AEs) will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by specified time periods in order to understand the evolution of TEAEs over time. Additionally, the pre-specified TEAEs and SAEs that may be associated with physical dependence will be summarized separately. An overview of AEs, which includes subject incidence of TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Summary statistics for actual safety laboratory values and for changes from baseline will be tabulated 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. A listing of all out-of-range laboratory test results, including assessment of clinical significance will also be provided. The observed vital sign data and change from baseline will be summarized with descriptive statistics and presented in a listing. The overall ECG assessment (abnormal or normal) and parameters will be summarized along with a summary of how many subjects developed a post-treatment abnormal result and will be presented in a listing. Physical exam findings will be recorded by the sites within medical history or AEs and otherwise not summarized, with the exception of weight, and change from baseline in weight. The WI-NRS, PROMIS-PIQ, DLQI, and IGA PN-S, will be summarized with descriptive statistics by visit.
Study Sites:	Approximately 120 study sites
Expected Duration of Subject's Participation	Approximately 56 weeks: 52 weeks of treatment, and a post-drug observation period of 4 weeks.

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

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LIST OF APPENDICES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CYP3A4	cytochrome-P 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
FSH	Follicle-stimulating hormone
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor
NRS	Numeric rating scale
PI	Principal Investigator
PK	Pharmacokinetics
PROMIS-PIQ	Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PIQ)
PN	Prurigo nodularis
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus

Pruritus, or itch, is defined as an unpleasant sensation that evokes a desire to scratch (Ikoma 2006). Itch and pain, although closely related, are distinct sensations: itch elicits a scratching response, whereas pain causes a withdrawal response.

Emerging research in neurobiology has greatly expanded the understanding of pruritus signaling. Pruritoceptors (itch-sensory nerve fibers) consist of two distinct classes of nerve fibers: histamine-responsive mechanoinsensitive C-fibers, and histamine-unresponsive mechanosensitive polymodal C and Aδ fibers that are activated by cowhage (highly pruritic spicules from the pods of the cowhage plant *Mucuna pruriens*) (Schmelz 2015). The second class of histamine-unresponsive, cowhage-responsive nerve fibers has been of particular interest in pruritus research, as C-fibers that have a strong and sustained response to histamine comprise only about 20% of the overall mechanoinsensitive C-fiber population (Steinhoff 2006), and a significant proportion of chronic pruritic conditions do not appear to involve histamine-mediated pruritus signaling (Ikoma 2006). Substance P (SP) is a prominent pruritogen (itch mediator) in this histamine-independent pruritus pathway (Chuquilin 2016).

Pruritus stimuli in the skin are transmitted via sensory neurons that have their cell bodies in the dorsal root ganglia (DRG) and are linked to second-order neurons in the spine (Carstens 2016, Luo 2015). Following activation of these DRG sensory neurons, the pruritus signal is transmitted to the second-order spinal neurons primarily by SP, gastrin-releasing peptide, and glutamate in histamine-independent pruritus, and primarily by glutamate in histamine-mediated pruritus (Chuquilin 2016).

Spinal itch neuron projections ascend via the contralateral spinothalamic tract to the thalamus and via the lateral spinoparabrachial tract to the lateral parabrachial nucleus, from which point they activate multiple centers in the somatosensory cortex, the premotor cortex, and the cingulate cortex – areas involved in the sensory processing and motor response (scratching) to the itch signal (Carstens 2016, Chuquilin 2016).

1.1.1 Role of Substance P and the Neurokinin-1 Receptor in Pruritus

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 (NK_1-R), neurokinin-2, and neurokinin-3 receptors (Harrison 2001). The neurokinin-1 receptor, in particular, has been studied in great detail. NK_1-R is the primary receptor for SP in the human body, and is found on multiple cell types, including central and peripheral neurons, keratinocytes, mast cells, and dendritic cells (El-Nour 2006, Ständer 2015).

NK_1-R 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-R 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).

1.2 Serlopitant

1.2.1 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 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.

1.2.2 Serlopitant Clinical Summary

In humans, serlopitant has been administered to over 1000 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 males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young and elderly subjects. A single loading dose of up to 15 mg followed by 6 to 8 weeks of up to 5 mg daily doses has been well tolerated in adults with chronic pruritus and prurigo nodularis (PN).

Pharmacokinetic data demonstrate good plasma exposures with oral dosing, linear dose-dependent increases in plasma concentration and systemic exposure, a plasma t1/2 appropriate for 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 CCI, M2/M2a CCI, and M3 CCI. 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.

1.2.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

TCP-101 was a double-blind, placebo-controlled, multi-center study that compared serlopitant 0.25 mg, 1 mg, or 5 mg vs. placebo for the treatment of chronic pruritus. A total of 257 adult subjects 18-65 years of age with chronic pruritus were randomized to receive one of the four dose groups in a 1:1:1:1 randomization. Subjects received a loading dose of 3 tablets on Day 1 and thereafter received 1 tablet per day for 6 weeks. The primary efficacy endpoint was itch severity as measured on a Visual Analog Scale (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 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 of the percentage of subjects who were 4-point responders on average VAS at Week 8, 25.0% of placebo subjects and 54.4% of serlopitant subjects were 4-point responders.

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

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

The results of the Phase 2 studies in PN and chronic pruritus, together with the extensive nonclinical and clinical safety data and 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 long-term treatment of pruritus in patients with PN, AD, or psoriasis. The potential benefits of continued clinical study outweigh the potential risks. The data obtained from this long-term study will inform the risks and benefits of long-term exposure (chronic or repeated intermittent use for longer than 6 months). The risk to subjects in this study will be minimized by medical and safety monitoring (see Section 3.4.1).

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

2 STUDY OBJECTIVES

The primary objective of this study is to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis.

The secondary objectives of this study are to assess the change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS); to assess the change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN; and to assess whether serlopitant produces physical dependence.

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. Approximately 120 study sites may enroll subjects in this long-term safety study.

This study will consist of two periods, for a total study period of approximately 56 weeks:

- Treatment period: 52 weeks
- Post-drug observation period: 4 weeks

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally (Section 5.3).

Standard therapy for the concurrent skin lesions and pruritus may be employed during this study (Section 5.7.1).

The WI-NRS during a 24-hour recall period will be assessed by the subject at each study visit.

For those subjects with PN, the severity and extent of PN will be assessed at selected visits, using the IGA-PN-S, and photographs of representative areas with PN will be taken at selected visits at a subset of sites.

The Patient-Reported Outcomes Measurement Information System Itch Questionnaire (PROMIS-PIQ) and the Dermatology Life Quality Index (DLQI) will be administered at selected visits.

After completion of the 52-week treatment period, all subjects will enter a 4-week post-drug observation period. Subjects who discontinue treatment early will have a post-drug observation visit 4 weeks after their last dose of serlopitant. During this monitored discontinuation period, solicited safety evaluations will assess the potential for serlopitant to produce physical dependence.

3.2 Rationale for Study Design and Dose Selection

The current MTI-107 study is designed to confirm the long-term safety of serlopitant for the treatment of pruritus in patients with PN, AD, and psoriasis. The 5 mg dose of serlopitant was selected for this study based on the favorable efficacy, safety, and tolerability profile of serlopitant at this dose level in completed studies.

3.3 Study Endpoints

3.3.1 Safety Endpoints

The 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
- Assessment of physical dependence following chronic study drug exposure, in the 4-week post-drug discontinuation period.

3.3.2 Efficacy Endpoints

The efficacy endpoints are as follows:

- Changes from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52

- Changes from baseline in PROMIS-PIQ score for Itch (General, Scratching Behavior, Mood and Sleep, Activity and Clothing) to Weeks 20, 36, and 52
- Changes from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Changes from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52

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 safety data on a regular basis throughout the study.

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 400 adult subjects with pruritus due to PN, AD, or psoriasis will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. Subject reports pruritus in the 24-hour period prior to enrollment and:
   a. Has completed a prior applicable clinical study of serlopitant without an SAE that was assessed as likely related to the study drug

      OR

   b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and Sponsor has approved enrollment.
3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year, refer to section 7.1.5 for acceptable methods of contraception) from the time of the Baseline visit until 2 weeks after last dose of study drug.
4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies).
2. Presence of a psychiatric diagnosis (such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol abuse disorder) meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria in past 3 years, history of suicidal ideation within the past 3 years or any history of suicide attempt.
3. Presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject.
4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107.
5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment.
6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment (Appendix B).
7. Currently pregnant or breastfeeding or planning to become pregnant during the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

The study drug in this study is serlopitant 5 mg 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 study drug will be provided in bottles that can be stored at room temperature (59-86°F, 15-30°C).

Each bottle will each contain 18 serlopitant tablets.

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

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Subjects will be instructed to take all doses from Baseline Visit (Study Day 1) until the Week 52 Visit, once a day and not within 2 hours before or after a meal.

Should the study drug be withheld (without intent to discontinue study drug, Section 5.6), the drug may be resumed at the discretion of the investigator, at the same dosing regimen.

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

Each dose of study drug after the first dose must be administered once daily, and not within 2 hours before or after a meal. If a dose is missed, that dose will be considered and documented as a missed dose. Dosing should resume as directed the next day.

5.6 Study Drug Discontinuation

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

- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion
- Baseline serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) (exception may be made for retesting within 28 days of enrollment as approved by the Medical Monitor)
- A female subject becomes pregnant
- The subject decides to discontinue study drug, or withdraws consent from the study
- The subject reports use of a strong CYP3A4 inhibitor (as listed in Appendix B) within 4 weeks of the study visit at which it was reported, initiates any investigational medication, or other NK_1-R antagonist (exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)

- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion

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

Subjects who discontinue study drug prior to completing the treatment period will enter a 4-week follow-up period following the last dose of study drug (Section 6.4.10). Every effort should be made for subjects to complete this follow-up visit after a subject has discontinued from study drug.

5.7 Concomitant and Excluded Therapies

Concomitant therapies include any therapies (including over-the-counter medications) used by a subject from initiation of study drug 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 and routine preventative immunizations.

5.7.1 Excluded Therapies

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

- NK_1-R antagonists (other than study drug, exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)
- Strong CYP3A4 inhibitors (See Appendix B; exceptions may be made for use within 4 weeks of the study visit at which it was reported)
- Any investigational drug therapy other than serlopitant

Use of any excluded therapies should be reported as soon as possible, and will be recorded as protocol deviations for subjects who receive them. Subjects may be discontinued from the study drug (Section 5.6).

5.8 Assignment to Treatment

Eligible subjects will receive serlopitant 5 mg tablets.

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. Missed doses will be recorded as reported by the subject. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

6 STUDY SCHEDULE AND ASSESSMENTS

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

The Itch NRS is a validated, self-reported instrument for measurement of itch intensity. WI-NRS scores will be captured as per Appendix A. Subjects are asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicate greater itch intensity. In this study, WI-NRS during a 24-hour recall period prior to the specified visit will be captured.

6.1.2 Investigator's Global Assessment of PN Stage

The IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA PN-S uses clinical characteristics including the number of nodules and their thickness, as guidelines for the overall severity assessment. IGA PN-S scores will be captured as per Appendix A. Each assessment during the study must be done by the principal investigator (PI) or designee. Every effort should be made to ensure that all assessments for a given subject are done by the same individual throughout the study. However, a change in assessor for a given subject, though not ideal, will not be considered a protocol deviation.

6.1.3 Patient-Reported Outcomes Measurement Information System Itch Questionnaire

PROMIS-PIQ is an itch-specific instrument that measures quality of life impairment related to itch in the previous week. The PROMIS-PIQ includes 4 domains (General, Scratching Behavior, Mood and Sleep, and Activity and Clothing). Subjects will complete the PROMIS-PIQ short forms as per Appendix A.

6.1.4 Dermatology Life Quality Index

DLQI is a dermatology specific quality of life instrument designed to assess the impact of the skin disease on a subject's quality of life over the prior week. It is a ten-item questionnaire that assesses overall quality of life (QOL) and six aspects that may affect QOL (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment). The DLQI questionnaire will be collected as per Appendix A.

6.1.5 Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as per Appendix A. These areas may include the extensor surfaces of both arms and both legs (overview of both legs, detail of lower legs), and the abdomen and back. The central photography vendor will provide photographic equipment to the sites for use during the study. Detailed instructions will be provided in a Photography Manual.

6.2 Safety Parameters

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

6.2.1 Vital Signs

Vital signs will include measurements of heart rate, 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 as per Appendix A and at unscheduled study visits when clinically indicated. When possible, assessment of vital signs should precede blood draw.

6.2.2 Physical Examination

Physical examinations will be performed as per Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the Baseline visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. The subjects' height and weight will be measured as per Appendix A.

6.2.3 Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected as per Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified. When possible, blood draws should follow ECGs and vital sign measurements if they occur on the same visit.

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

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, uric acid, total protein, alanine

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel

- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)

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. When possible, ECGs should precede measurement of vital signs and blood draw for clinical laboratory tests. ECGs will be performed as per Appendix A and at unscheduled study visits when clinically indicated. ECGs will be reviewed and reported by a central ECG vendor. The ECG machine and detailed instructions will be provided by the ECG vendor.

6.2.5 Assessment of Potential for Physical Dependence

NK_1-R antagonist dependence has not previously been described and therefore a drug class-specific, reliable and sensitive instrument for the assessment of withdrawal symptoms has not been developed. A surrogate assessment tool, such as those developed for opioid or benzodiazepine dependence, is not available.

In the statistical analysis plan (SAP), the Sponsor will specify a targeted medical event list (TEAEs) that may be associated with physical dependence, and evaluate reports of these events in the monitored 4-week post-drug discontinuation period.

6.3 Subject Flow Diagram

The visit schedule and assessments are summarized in Appendix A.

6.4 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 and 6.2. The timing of each study visit is relative to the day of enrollment (Baseline Visit).

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

6.4.1 Baseline Visit

The Baseline Visit may coincide with the final visit of the MTI-103, MTI-105, MTI-106, or MTI-109 studies.

The following procedures are to be performed at the Baseline Visit (Day 1):

- Obtain written informed consent prior to any protocol-mandated procedures (must be obtained prior to any other assessments)
- Confirm subject's eligibility based on the inclusion/exclusion
- Collect demographic information (when permitted by regional laws or guidelines: sex, date of birth, race/ethnicity)
- Collect any concomitant medications
- Review and record subject's medical history, including ongoing TEAEs from prior study (if applicable)
- Perform complete physical examination (including height and weight)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (exception: participants in MTI-103, MTI-105, MTI-106, and MTI-109 who have had these labs in prior 14 days, in the context of that study)
  - Hematology
  - Chemistry
  - Reproductive endocrine labs for females under 55 years of age at consent
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Register Baseline Visit into the Interactive Web Response System (IWRS)
- Dispense study drug
- Confirm next scheduled visit date

6.4.2 Week 4 Visit

The Week 4 Visit occurs 28 days (±7 days) after the Baseline Visit. At the Week 4 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.3 Week 8 Visit

The Week 8 Visit occurs 56 days (±7 days) after the Baseline Visit. At the Week 8 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)

- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.4 Week 12 Visit

The Week 12 Visit occurs 84 days (±7 days) after the Baseline Visit. At the Week 12 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.5 Week 20 Visit

The Week 20 Visit occurs 140 days (±7 days) after the Baseline Visit. At the Week 20 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.6 Week 28 Visit

The Week 28 Visit occurs 196 days (±7 days) after the Baseline Visit. At the Week 28 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Hematology
  - Chemistry

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.7 Week 36 Visit

The Week 36 Visit occurs 252 days (±7 days) after the Baseline Visit. At the Week 36 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.8 Week 44 Visit

The Week 44 Visit occurs 308 days (±7 days) after the Baseline Visit. At the Week 44 Visit, the following procedures and assessments are to be performed:

- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.9 Week 52 Visit

The Week 52 Visit occurs 364 days (±7 days) after the Baseline Visit. At the Week 52 Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Hematology
  - Chemistry

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Confirm next scheduled visit date

6.4.10 Early Treatment Discontinuation Visit/Post-Drug Observation

The Early Treatment Discontinuation (ETD) Visit occurs within 28 days of last dose for subjects who discontinue serlopitant treatment prior to Week 52.

The Post-Drug Observation Visit occurs 28 days (±7 days) after the Week 52 Visit.

At the ETD/Post-Drug Observation Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Assess and record any AEs and/or SAEs
- Assess and record any changes in the subject's concomitant medications
- Perform targeted physical examination with weight
- Obtain ECG (ETD only)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Ask subject to complete WI-NRS

- Ask the subject to complete the following questionnaires (ETD only):
  - PROMIS-PIQ
  - DLQI
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography, ETD only)
- Collect returned study drug (ETD only)

6.4.11 Early Termination

Early termination of a subject from the study may occur due to loss to follow-up or withdrawal of consent by the subject. In accordance with legal requirements and International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If 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). Attempts to contact subjects who are suspected of being lost to follow-up 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 not considered SAEs: a visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event), an elective surgery planned prior to signing consent, admission as per protocol for planned medical/surgical procedure, and/or routine health assessments requiring admission for baseline/trending of health status (e.g. routine colonoscopy).

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

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

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

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

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

If the clinically significant laboratory, vital sign, or ECG abnormality is a sign associated with a confirmed disease or condition (e.g. elevated creatinine in a subject diagnosed with

chronic kidney disease), only the diagnosis (chronic kidney disease) needs to be recorded on the AE eCRF (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; a post-menopausal 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
3. Hormonal contraception associated with consistent inhibition of ovulation; these may include (but are not necessarily limited to) oral, intravaginal, implantable, injectable, or transdermal delivery methods.
    a. Progesterone only oral contraceptives are excluded as a highly effective method, as they do not consistently inhibit ovulation.
4. Intrauterine device/system
5. Exclusive monogamous intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner

Any pregnancy occurring in a female subject or the female partner of a male subject, from the first study drug administration through the 4-week 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 or Underlying Pruritic Skin Disease

Pruritus or the underlying pruritic skin disease (PN, AD, or psoriasis) 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. It is important to include a description of the nature of the unexpected worsening when recording the AE or SAE (e.g. new PN lesions in previously uninvolved skin).

7.2 Methods and Timing for Recording and Reporting Adverse Events

7.2.1 Adverse Event Reporting Period

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

AEs and SAEs will be recorded from the first study drug administration through the follow-up visit. After the 4-week follow-up visit, only SAEs that are believed to be drug-related should be reported.

After informed consent, 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 Baseline visit procedures but are not enrolled into the study will not have SAEs recorded in the clinical database.

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

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

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

Table 1 Adverse Event Grading

Grade	Severity	Alternate Description[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) v4.03

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 treatment with study drug or participation in the study is not the cause of the AE or SAE.

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

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

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

Please see the 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 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.

8 STATISTICAL METHODS

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

Baseline will be the last recorded value prior to the start of treatment.

A SAP describing all statistical analyses will be written as a separate document.

8.1 Handling of Missing Data and Excluded Therapy Use

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

8.2 Analysis Population

All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population.

8.3 Subject Disposition

An accounting of all 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.

8.4 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.5 Concomitant Medications

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

8.6 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.

8.7 Efficacy Analyses

Descriptive statistics will be used to summarize the following:

- Changes from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Changes from baseline in PROMIS-PIQ score for Itch (General, Scratching Behavior, Mood and Sleep, Activity and Clothing) to Weeks 20, 36, and 52
- Changes from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Changes from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52.

Data will be summarized by time point using frequency tabulations or descriptive statistics as appropriate. Observed results, as well as change from baseline will be summarized, as appropriate.

8.8 Safety Analyses

8.8.1 Adverse Events

All AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by time period in order to understand the evolution of TEAEs over time. Thus, in addition to the TEAE analysis over the entire 12-month treatment time, results will be presented for the following periods: 0 to 4 weeks, > 4 to 12 weeks, > 12 to 28 weeks, > 28 weeks to 36 weeks, > 36 to end of treatment, and end of treatment to end of the study. Additionally, the pre-specified TEAEs and SAEs that may be associated with physical dependence will be summarized separately. For incidence reporting, if a subject reported more than one TEAE 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, TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, end date (if ended), seriousness, severity, action taken regarding the study drug, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided.

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

8.8.2 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, and listings will be provided.

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. A listing of all out-of-range laboratory test results, including assessment of clinical significance, will also be provided.

8.8.3 Vital Signs

The observed vital sign data and change from baseline for each scheduled visit will be summarized with descriptive statistics, and presented in a listing.

8.8.4 Electrocardiograms

The overall ECG assessment (abnormal or normal) and parameters will be summarized along with a summary of how many subjects developed a post-treatment abnormal result, and will be presented in a listing.

8.8.5 Physical Exams

Physical exam findings will be recorded by the sites within medical history or adverse events and otherwise not summarized, with the exception of weight and change from baseline in weight.

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. A written statement fully documenting the reasons for study termination will be provided to the IRB or EC.

9.3 Monitoring and Auditing Procedures

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

9.4 Transfer of Obligations

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

9.5 Informed Consent

The purpose of the study, the procedures to be carried out, and any potential risks of study participation will be described in non-technical terms in the ICF. After having reviewed and understood the ICF, subjects will be required to read, sign, and date an IRB-approved or EC-approved consent form before any study-specific procedures are carried out. Subjects 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(R2) 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, Investigator Brochure, 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 and ECG data will be recorded in an eCRF system. Data will be entered at the site by the appropriately designated and trained site personnel. All source documents from which eCRF entries are derived should be placed in the subject's medical records. eCRFs will be completed for every subject screened in the study. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

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(R2) guideline and the site's data retention policies. These records must be available for inspection by the Sponsor, monitor, and regulatory authorities. Furthermore, the investigators/institutions will permit trial-related monitoring, audits, EC review, and inspections by a competent authority as necessary and provide direct access to source data/documents.

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

9.9 Good Clinical Practice and Ethical Study Conduct

The study procedures outlined in this protocol will be conducted in accordance with applicable ICH Guidelines, including ICH E6(R2): Good Clinical Practice. 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

Examination	Baseline[1]	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 20 (±7 days)	Week 28 (±7 days)	Week 36 (±7 days)	Week 44 (±7 days)	Week 52 (±7 days)	Early Treatment Discontinuation	Post-drug observation[2]
Informed consent	X										
I/E criteria	X										
Demographics/ Medical History	X										
Physical exam[3]	X[4]	X	X	X	X	X	X	X	X	X[4]	X[4]
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Labs[5]	X[1]	X		X		X			X	X	X
Urine pregnancy test[6]	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X		X		X	X	
WI-NRS	X	X	X	X	X	X	X	X	X	X	X
IGA PN-S (PN subjects only)	X	X	X	X	X	X	X	X	X	X	X
PROMIS-PIQ and DLQI	X				X		X		X	X	
Photographs (if applicable)	X				X		X		X	X	
Dispense and/or collect serlopitant	X	X	X	X	X	X	X	X	X	X	
Review study drug compliance		X	X	X	X	X	X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X

1 Baseline may coincide with the final visit of prior applicable study; Baseline labs do not need to be repeated if completed within prior 14 days

2 The post-drug observation visit occurs 28 days (± 7 days) after the Week 52 visit

3 Baseline physical exam is complete; all other physical exams are targeted

4 Height/weight at Baseline and weight at ETD/post-drug

5 Hematology and Chemistry at Baseline, Weeks 4, 12, 28, 52 and ETD/post/drug; Reproductive Endocrinology at Baseline, Weeks 28 and 52 (females under 55 years of age at consent)

6 For females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

The list of strong CYP3A4 inhibitors is based on the United States Food and Drug Administration (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. regular grapefruit juice consumption
9. idelalisib
10. indinavir and ritonavir
11. itraconazole[a]
12. ketoconazole[a]
13. lopinavir and ritonavir
14. nefazodone
15. nelfinavir
16. paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
17. posaconazole[a]
18. ritonavir
19. saquinavir and ritonavir
20. telaprevir
21. tipranavir and ritonavir
22. troleandomycin
23. voriconazole[a]

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

CLINICAL STUDY PROTOCOL MTI-107

SUMMARY OF CHANGES

Drug Product Name: Serlopitant

Study Title: MTI-107: AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS

Version: 1.1

Release Date: 11 April 2018

Replaces Previous Version: 1.0 (Dated 18 December 2017)

OVERVIEW:

MTI-107 protocol was amended to include language regarding the potential benefit and potential risk for the participating patients as well as the assessment of the ratio of this benefit and risk based on receipt of BfArM Deficiency Letter dated 20 March 2018.

KEY CHANGES: N/A

ADMINISTRATIVE CHANGES:

Section(s)	Summary of Change
1.2.3 Serlopitant in Pruritus-Related Studies	Amended to include language regarding the potential benefit and potential risk for the participating patients as well as the assessment of the ratio of this benefit and risk
Throughout	Updated protocol version in the footer

CLINICAL STUDY PROTOCOL

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
ClinicalTrials.gov ID:	NCT03540160
Protocol No.:	MTI-107
Protocol Version/Date:	Version 2.0/03 July 2018
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063**,** USA

Confidentiality Statement:

SIGNATURE PAGE FOR INVESTIGATOR(S)

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
ClinicalTrials.gov ID:	NCT03540160
Protocol No.:	MTI-107
Protocol Version/Date:	Version 2.0/03 July 2018
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063**,** USA

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

_____
Principal Investigator's printed name

_____ _____
Principal Investigator's signature Date (DD-MMM-YYYY)

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
ClinicalTrials.gov ID:	NCT03540160
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Protocol Version/Date:	Version 2.0/03 July 2018
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063, USA

Approved by:

PPD

Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Study Title:	An Open-Label Long-Term Safety Study of Serlopitant for the Treatment of Pruritus
Protocol Number:	MTI-107
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Primary objective: • To assess the long-term safety of serlopitant in adults with pruritus associated with prurigo nodularis (PN), atopic dermatitis (AD), or psoriasis. Secondary objectives: • To assess change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS). • To assess change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN. • To assess whether serlopitant produces physical dependence.
Study Design:	Study MTI-107 is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. The study will consist of two periods, for a total study period of approximately 57 weeks: • Treatment period: 52 weeks • Post-drug observation period: 5 weeks During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Standard therapy for the concurrent skin lesions and pruritus may be employed during this study. After completion of the 52-week treatment period, all subjects will enter a 5-week post-drug observation period. Subjects who discontinue treatment early will have post-drug observation visits through 5 weeks after their last dose of serlopitant.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 400 subjects
Study Population:	The study will enroll adults with pruritus associated with PN, AD, or psoriasis. Inclusion Criteria (Subjects must meet the following criteria to be enrolled into the study): 1. Male or female, age 18 years or older at consent. 2. Subject reports pruritus in the 24-hour period prior to enrollment and: a. Has completed a prior applicable clinical study of serlopitant without a serious adverse event (SAE) that was assessed as likely related to the study drug. (For participants from study TCP-102,

	the WI-NRS score must be ≥ 7 in the 24-hour period prior to the Baseline visit.) OR b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and has a WI-NRS score ≥ 7 in the 24-hour period prior to the Baseline visit, and Sponsor has approved enrollment. 3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year) from the time of the Baseline visit until 5 weeks after last dose of study drug. 4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies). 2. Any known major psychiatric diagnosis, such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder, which may confound the assessment of serlopitant safety or efficacy, or interfere with the subject's ability to comply with protocol-mandated activities, within 3 years prior to enrollment. 3. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy; or the presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject. 4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107. 5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment. 6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment. 7. Currently pregnant or breastfeeding or planning to become pregnant during the study.
Study Drug:	Serlopitant 5 mg tablets
Dosage:	Serlopitant: 5 mg once daily orally for 52 weeks
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) and SAEs • Change from baseline in clinical laboratory parameters following study drug exposure • Change from baseline in vital sign and electrocardiogram (ECG) parameters following study drug exposure

	• Change from baseline in the Hospital Anxiety and Depression Scale (HADS) • Change from baseline in the Epworth Sleepiness Scale (ESS) • Assessment of physical dependence following chronic study drug exposure, in the monitored 5-week post-drug discontinuation period
Efficacy Endpoints:	• Change from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52 • Change from baseline in Dermatology Life Quality Index (DLQI) (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52 • Change from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52
Statistical Methods:	All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population. Data will be summarized with descriptive statistics by visit. For continuous variables, the following information will be presented: n, mean, standard deviation, median, minimum and maximum. For categorical variables, counts and percentages will be used. All adverse events (AEs) will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by specified time periods in order to understand the evolution of TEAEs over time. An overview of AEs, which includes subject incidence of TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Summary statistics for actual safety laboratory values and for changes from baseline will be tabulated 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. A listing of all out-of-range laboratory test results, including assessment of clinical significance will also be provided. The observed vital sign data and change from baseline will be summarized with descriptive statistics and presented in a listing. 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. Physical exam findings will be recorded by the sites within medical history or AEs and otherwise not summarized, with the exception of weight, and change from baseline in weight. The WI-NRS, DLQI, and IGA PN-S will be summarized with descriptive statistics by visit. Summary statistics for the HADS and ESS actual values and change from baseline will be presented by scheduled visit.

Study Sites:	Approximately 120 study sites
Expected Duration of Subject's Participation	Approximately 57 weeks: 52 weeks of treatment, and a post-drug observation period of 5 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone, corticotropin
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CYP3A4	Cytochrome P-450 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ESS	Epworth Sleepiness Scale
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
FSH	Follicle-stimulating hormone
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor
NRS	Numeric rating scale
PI	Principal Investigator
PK	Pharmacokinetics
PN	Prurigo nodularis
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus

Pruritus, or itch, is defined as an unpleasant sensation that evokes a desire to scratch (Ikoma 2006). Itch and pain, although closely related, are distinct sensations: itch elicits a scratching response, whereas pain causes a withdrawal response.

Emerging research in neurobiology has greatly expanded the understanding of pruritus signaling. Pruritoceptors (itch-sensory nerve fibers) consist of two distinct classes of nerve fibers: histamine-responsive mechanoinsensitive C-fibers, and histamine-unresponsive mechanosensitive polymodal C and Aδ fibers that are activated by cowhage (highly pruritic spicules from the pods of the cowhage plant *Mucuna pruriens*) (Schmelz 2015). The second class of histamine-unresponsive, cowhage-responsive nerve fibers has been of particular interest in pruritus research, as C-fibers that have a strong and sustained response to histamine comprise only about 20% of the overall mechanoinsensitive C-fiber population (Steinhoff 2006), and a significant proportion of chronic pruritic conditions do not appear to involve histamine-mediated pruritus signaling (Ikoma 2006). Substance P (SP) is a prominent pruritogen (itch mediator) in this histamine-independent pruritus pathway (Chuquilin 2016).

Pruritus stimuli in the skin are transmitted via sensory neurons that have their cell bodies in the dorsal root ganglia (DRG) and are linked to second-order neurons in the spine (Carstens 2016, Luo 2015). Following activation of these DRG sensory neurons, the pruritus signal is transmitted to the second-order spinal neurons primarily by SP, gastrin-releasing peptide, and glutamate in histamine-independent pruritus, and primarily by glutamate in histamine-mediated pruritus (Chuquilin 2016).

Spinal itch neuron projections ascend via the contralateral spinothalamic tract to the thalamus and via the lateral spinoparabrachial tract to the lateral parabrachial nucleus, from which point they activate multiple centers in the somatosensory cortex, the premotor cortex, and the cingulate cortex – areas involved in the sensory processing and motor response (scratching) to the itch signal (Carstens 2016, Chuquilin 2016).

1.1.1 Role of Substance P and the Neurokinin-1 Receptor in Pruritus

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 (NK_1-R), neurokinin-2, and neurokinin-3 receptors (Harrison 2001). The neurokinin-1 receptor, in particular, has been studied in great detail. NK_1-R is the primary receptor for SP in the human body, and is found on multiple cell types, including central and peripheral neurons, keratinocytes, mast cells, and dendritic cells (El-Nour 2006, Ständer 2015).

NK_1-R 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-R 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).

1.2 Serlopitant

1.2.1 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.

1.2.2 Serlopitant Clinical Summary

In humans, serlopitant has been administered to over 1000 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 males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young and elderly subjects. A single loading dose of up to 15 mg followed by 6 to 8 weeks of up to 5 mg daily doses has been well tolerated in adults with chronic pruritus and prurigo nodularis (PN).

Pharmacokinetic data demonstrate good plasma exposures with oral dosing, linear dose-dependent increases in plasma concentration and systemic exposure, a plasma t1/2 appropriate for 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 CCI, M2/M2a CCI, and M3 CCI. 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.

1.2.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

TCP-101 was a double-blind, placebo-controlled, multi-center study that compared serlopitant 0.25 mg, 1 mg, or 5 mg vs. placebo for the treatment of chronic pruritus. A total of 257 adult subjects 18-65 years of age with chronic pruritus were randomized to receive one of the four dose groups in a 1:1:1:1 randomization. Subjects received a loading dose of 3 tablets on Day 1 and thereafter received 1 tablet per day for 6 weeks. The primary efficacy endpoint was itch severity as measured on a Visual Analog Scale (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 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 of the percentage of subjects who were 4-point responders on average VAS at Week 8, 25.0% of placebo subjects and 54.4% of serlopitant subjects were 4-point responders.

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

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

The results of the Phase 2 studies in PN and chronic pruritus, together with the extensive nonclinical and clinical safety data and 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 long-term treatment of pruritus in patients with PN, AD, or psoriasis. The potential benefits of continued clinical study outweigh the potential risks. The data obtained from this long-term study will inform the risks and benefits of long-term exposure (chronic or repeated intermittent use for longer than 6 months). The risk to subjects in this study will be minimized by medical and safety monitoring (see Section 3.4.1).

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

2 STUDY OBJECTIVES

The primary objective of this study is to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis.

The secondary objectives of this study are to assess the change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS); to assess the change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN; and to assess whether serlopitant produces physical dependence.

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. Approximately 120 study sites may enroll subjects in this long-term safety study.

This study will consist of two periods, for a total study period of approximately 57 weeks:

- Treatment period: 52 weeks
- Post-drug observation period: 5 weeks

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally (Section 5.3).

Standard therapy for the concurrent skin lesions and pruritus may be employed during this study (Section 5.7.1).

The WI-NRS during a 24-hour recall period will be assessed by the subject at each study visit.

For those subjects with PN, the severity and extent of PN will be assessed at selected visits, using the IGA-PN-S, and photographs of representative areas with PN will be taken at selected visits at a subset of sites.

The Dermatology Life Quality Index (DLQI) will be administered at selected visits.

After completion of the 52-week treatment period, all subjects will enter a 5-week post-drug observation period. Subjects who discontinue treatment early will have a post-drug observation visit through 5 weeks after their last dose of serlopitant. During this monitored discontinuation period, solicited safety evaluations will assess the potential for serlopitant to produce physical dependence.

3.2 Rationale for Study Design and Dose Selection

The current MTI-107 study is designed to confirm the long-term safety of serlopitant for the treatment of pruritus in patients with PN, AD, and psoriasis. The 5 mg dose of serlopitant was selected for this study based on the favorable efficacy, safety, and tolerability profile of serlopitant at this dose level in completed studies.

3.3 Study Endpoints

3.3.1 Safety Endpoints

The safety endpoints are as follows:

- Incidence of TEAEs and SAEs
- Change from baseline in clinical laboratory parameters
- Change from baseline in vital sign and ECG parameters
- Change from baseline in the Hospital Anxiety and Depression Scale (HADS)
- Change from baseline in the Epworth Sleepiness Scale (ESS)
- Assessment of physical dependence following chronic study drug exposure, in the 5-week post-drug discontinuation period.

3.3.2 Efficacy Endpoints

The efficacy endpoints are as follows:

- Change from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Change from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Change from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52

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 safety data on a regular basis throughout the study.

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 400 adult subjects with pruritus associated with PN, AD, or psoriasis will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. Subject reports pruritus in the 24-hour period prior to enrollment and:
    a. Has completed a prior applicable clinical study of serlopitant without an SAE that was assessed as likely related to the study drug (For participants from study TCP-102, the WI-NRS score must be ≥ 7 in the 24-hour period prior to the Baseline visit.)

    OR

    b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and has a WI-NRS score ≥ 7 in the 24-hour period prior to the Baseline visit, and Sponsor has approved enrollment.
3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year, refer to Section 7.1.5 for acceptable methods of contraception) from the time of the Baseline visit until 5 weeks after last dose of study drug.
4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies).
2. Any known major psychiatric diagnosis, such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder, which may confound the assessment of serlopitant safety or efficacy, or interfere with the subject's ability to comply with protocol-mandated activities, within 3 years prior to enrollment.
3. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy; or the presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject.
4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107.
5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment.
6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment (Appendix B).
7. Currently pregnant or breastfeeding or planning to become pregnant during the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

The study drug in this study is serlopitant 5 mg 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 study drug will be provided in bottles that can be stored at room temperature (59-86°F, 15-30°C).

Each bottle will each contain 18 serlopitant tablets.

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

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Subjects will be instructed to take all doses from Baseline Visit (Study Day 1) until the Week 52 Visit, once a day. Study drug may be taken with or without food.

Should the study drug be withheld (without intent to discontinue study drug, Section 5.6), the drug may be resumed at the discretion of the investigator, at the same dosing regimen.

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

Each dose of study drug after the first dose must be administered once daily. If a dose is missed, that dose will be considered and documented as a missed dose. Dosing should resume as directed the next day.

5.6 Study Drug Discontinuation

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

- 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
- Baseline serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) (exception may be made for retesting within 28 days of enrollment as approved by the Medical Monitor)
- 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, or withdraws consent from the study
- The subject reports use of a strong CYP3A4 inhibitor (as listed in Appendix B) within 4 weeks of the study visit at which it was reported, initiates any investigational medication, or other NK_1-R antagonist (exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)
- 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 discontinuation due to an AE or pregnancy. Investigators should make every effort to contact the Sponsor or designee before discontinuing study drug, if possible.

Subjects who discontinue study drug prior to completing the treatment period will enter a 5-week follow-up period following the last dose of study drug (Section 6.4.10). Every effort should be made for subjects to complete this follow-up visit after a subject has discontinued from study drug.

5.7 Concomitant and Excluded Therapies

Concomitant therapies include any therapies (including over-the-counter medications) used by a subject from initiation of study drug 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 and routine preventative immunizations.

5.7.1 Excluded Therapies

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

- NK_1-R antagonists (other than study drug, exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)
- Strong CYP3A4 inhibitors (See Appendix B; exceptions may be made for use within 4 weeks of the study visit at which it was reported)
- Any investigational drug therapy other than serlopitant

Use of any excluded therapies should be reported as soon as possible, and will be recorded as protocol deviations for subjects who receive them. Subjects may be discontinued from the study drug (Section 5.6).

5.8 Assignment to Treatment

Eligible subjects will receive serlopitant 5 mg tablets.

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. Missed doses will be recorded as reported by the subject. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

6 STUDY SCHEDULE AND ASSESSMENTS

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

The Itch NRS is a validated, self-reported instrument for measurement of itch intensity. WI-NRS scores will be captured as per Appendix A. Subjects are asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicate greater itch intensity. In this study, the subject is asked to rate the intensity of their *worst* itch (WI-NRS) during a 24-hour recall period prior to the specified visit; the questionnaire is provided in Appendix C.

6.1.2 Investigator's Global Assessment of PN Stage

The IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 (clear) to 4 (severe), as provided in Appendix D. The IGA PN-S uses clinical characteristics including the number of nodules and their thickness, as guidelines for the overall severity assessment. IGA PN-S scores will be captured as per Appendix A. Each assessment during the study must be done by the principal investigator (PI) or designee. Every effort should be made to ensure that all assessments for a given subject are done by the same individual throughout the study. However, a change in assessor for a given subject, though not ideal, will not be considered a protocol deviation.

6.1.3 Dermatology Life Quality Index

DLQI is a dermatology specific quality of life instrument designed to assess the impact of the skin disease on a subject's quality of life over the prior week. It is a ten-item questionnaire that assesses overall quality of life (QOL) and six aspects that may affect QOL (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and

treatment), and is provided in Appendix E. The DLQI questionnaire will be collected as per Appendix A.

6.1.4 Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as per Appendix A. These areas may include the extensor surfaces of both arms and both legs (overview of both legs, detail of lower legs), and the abdomen and back. The central photography vendor will provide photographic equipment to the sites for use during the study. Detailed instructions will be provided in a Photography Manual.

6.2 Safety Parameters

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

6.2.1 Vital Signs

Vital signs will include measurements of heart rate, 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 as per Appendix A and at unscheduled study visits when clinically indicated. When possible, assessment of vital signs should precede blood draw.

6.2.2 Physical Examination

Physical examinations will be performed as per Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the Baseline visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. The subjects' height and weight will be measured as per Appendix A. For female subjects with targeted breast examinations, 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 as per Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified. When possible, blood draws should follow ECGs and vital sign measurements if they occur on the same visit.

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 (Baseline, Weeks 12, 28, and 52):

- 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, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel
- Endocrine: TSH, free T4, cortisol, corticotropin (adrenocorticotropic hormone, ACTH), prolactin
  - 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.
- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Monthly pregnancy testing can be performed in between visits (and recorded as an Unscheduled visit), and at any time per the investigator's discretion, and as required by local authorities (e.g. in Austria). Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)
- For participants from study TCP-102 or those who had not participated in a prior clinical study of serlopitant, additional optional studies for the etiology of PN (if applicable) will be supported through local procedural and/or laboratory assessments (test kits not supplied by Sponsor). Studies may include, but are not limited to, iron studies (ferritin, serum iron), serum IgE, hepatitis B and C serology, HIV testing, skin biopsy and pathology interpretation, urea breath test for *Helicobacter pylori*, and allergy testing (patch, prick, or blood testing); the investigator should discuss the need for such studies with the medical monitor during the Screening period

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. When possible, ECGs should precede measurement of vital signs and blood draw for clinical laboratory tests. ECGs will be performed as per Appendix A and at unscheduled study visits when clinically indicated. ECGs will be reviewed and reported by a central ECG vendor. The ECG machine and detailed instructions will be provided by the ECG vendor.

6.2.5 Hospital Anxiety and Depression Scale

The HADS is a QOL instrument designed to assess the severity of anxiety and depression over the prior week, developed in a hospital outpatient clinic, but also valid in community

settings and primary care medical practice. The questionnaire takes approximately 2 to 5 minutes to complete, and is provided in Appendix F. The HADS questionnaire will be collected as outlined in Appendix A.

6.2.6 Epworth Sleepiness Scale

The ESS is a QOL instrument intended to measure daytime sleepiness by use of a very short questionnaire. The questionnaire takes approximately 2 to 3 minutes to complete, and is provided in Appendix G. The ESS questionnaire will be collected as outlined in Appendix A.

6.2.7 Assessment of Potential for Physical Dependence

NK_1-R antagonist dependence has not previously been described and therefore a drug class-specific, reliable and sensitive instrument for the assessment of withdrawal symptoms has not been developed. A surrogate assessment tool, such as those developed for opioid or benzodiazepine dependence, is not available.

In order to provide a comprehensive set of assessments for physical dependence and withdrawal symptoms following chronic exposure to the study drug, the HADS and ESS instruments will be administered at baseline and throughout the study period, as well as 3-days and 7-days following the last dose of study drug, and then weekly throughout the 5-week post-study drug observation period. In addition, vital signs will be assessed at each post-study drug observation visit, and an ECG and laboratory analyses will be assessed at the 5-week post-study drug visit. All TEAEs reported during this period will be medically reviewed to assess for possible physical dependence or withdrawal signs or symptoms.

6.3 Subject Flow Diagram

The visit schedule and assessments are summarized in Appendix A.

6.4 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 and 6.2. The timing of each study visit is relative to the day of enrollment (Baseline Visit).

Unscheduled visits may be performed as necessary, and may include procedures or assessments deemed necessary by the investigator and to conduct monthly urine pregnancy testing on females of childbearing potential in between regularly scheduled visits.

Female subjects who report periodic menstruation will be asked to complete a menstrual diary (paper form) throughout the study.

6.4.1 Baseline Visit

The Baseline Visit may coincide with the final visit of the MTI-103, MTI-105, MTI-106, or MTI-109 studies.

The following procedures are to be performed at the Baseline Visit (Day 1):

- Obtain written informed consent prior to any protocol-mandated procedures (must be obtained prior to any other assessments)
- Confirm subject's eligibility based on the inclusion/exclusion
- Collect demographic information (when permitted by regional laws or guidelines: sex, date of birth, race/ethnicity)
- Collect any concomitant medications
- Review and record subject's medical history, including ongoing TEAEs from prior study (if applicable)
  - 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
- Perform complete physical examination (including height and weight)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (exception: participants in MTI-103, MTI-105, MTI-106, and MTI-109 who have had these labs in prior 14 days, in the context of that study)
  - Hematology
  - Chemistry
  - Endocrine
  - Reproductive endocrine labs for females under 55 years of age at consent
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Register Baseline Visit into the Interactive Web Response System (IWRS)

- Dispense study drug
- Provide a menstrual diary to female subjects who report periodic menstruation
- Confirm next scheduled visit date

6.4.2 Week 4 Visit

The Week 4 Visit occurs 28 days (±7 days) after the Baseline Visit. At the Week 4 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.3 Week 8 Visit

The Week 8 Visit occurs 56 days (±7 days) after the Baseline Visit. At the Week 8 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.4 Week 12 Visit

The Week 12 Visit occurs 84 days (±7 days) after the Baseline Visit. At the Week 12 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry

- Endocrine

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.5 Week 20 Visit

The Week 20 Visit occurs 140 days (±7 days) after the Baseline Visit. At the Week 20 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)

- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.6 Week 28 Visit

The Week 28 Visit occurs 196 days (±7 days) after the Baseline Visit. At the Week 28 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
  - Endocrine
  - Reproductive endocrine labs for females under 55 years of age at consent
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.7 Week 36 Visit

The Week 36 Visit occurs 252 days (±7 days) after the Baseline Visit. At the Week 36 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.8 Week 44 Visit

The Week 44 Visit occurs 308 days (±7 days) after the Baseline Visit. At the Week 44 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)

- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.9 Week 52 Visit

The Week 52 Visit occurs 364 days (±7 days) after the Baseline Visit. At the Week 52 Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology

- Chemistry
- Endocrine
- Reproductive endocrine labs for females under 55 years of age at consent

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Confirm next scheduled visit date

6.4.10 Early Treatment Discontinuation Visit

The Early Treatment Discontinuation (ETD) Visit occurs within 35 days of last dose for subjects who discontinue serlopitant treatment prior to Week 52.

At the ETD Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug

6.4.11 Post-Drug Observation Visits

There are six (6) post-drug observation visits.

The Post-Drug Observation Visits occur 3 days (±1 days), 7 days (±3 days), 14 days (±3 days), 21 days (±3 days), 28 days (±3 days), and 35 days (±3 days) after the Week 52 Visit.

At the Post-Drug Observation Visits, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight (Only required at post-drug observation visit 35 days after Week 52 visit)
- Obtain ECG (Only required at post-drug observation visit 35 days after Week 52 visit)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test) (Only required at post-drug observation visit 35 days after Week 52 visit)

- Draw blood for clinical laboratory tests (Only required at post-drug observation visit 35 days after Week 52 visit)
  - Hematology
  - Chemistry
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - HADS
  - ESS
- Register visit into the IWRS (Only at post-drug observation visit 35 days after Week 52 visit)

6.4.12 Early Termination

Early termination of a subject from the study may occur due to loss to follow-up or withdrawal of consent by the subject. In accordance with legal requirements and International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If 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). Attempts to contact subjects who are suspected of being lost to follow-up 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 or Underlying Pruritic Skin Disease

Pruritus or the underlying pruritic skin disease (PN, AD, or psoriasis) 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. It is important to include a description of the nature of the unexpected worsening when recording the AE or SAE (e.g. new PN lesions in previously uninvolved skin).

7.2 Methods and Timing for Recording and Reporting Adverse Events

7.2.1 Adverse Event Reporting Period

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

AEs and SAEs will be recorded from the first study drug administration through the follow-up visit. After the 5-week 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 Baseline visit procedures but are not enrolled into the study will not have SAEs recorded in the clinical database.

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

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

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

Table 1 Adverse Event Grading

Grade	Severity	Alternate Description[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) v4.03

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 treatment with study drug or participation in the study is not the cause of the AE or SAE.

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

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

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

Please see the 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 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.

8 STATISTICAL METHODS

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

Baseline will be the last recorded value prior to the start of treatment.

A SAP describing all statistical analyses will be written as a separate document.

8.1 Handling of Missing Data and Excluded Therapy Use

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

8.2 Analysis Population

All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population.

8.3 Subject Disposition

An accounting of all 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.

8.4 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.5 Concomitant Medications

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

8.6 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.

8.7 Efficacy Analyses

Descriptive statistics will be used to summarize the following:

- Change from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Change from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Change from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52.

Data will be summarized by time point using frequency tabulations or descriptive statistics as appropriate. Observed results, as well as change from baseline will be summarized, as appropriate.

8.8 Safety Analyses

8.8.1 Adverse Events

All AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by time period in order to understand the evolution of TEAEs over time. Thus, in addition to the TEAE analysis over the entire 12-month treatment time, results will be presented for the following periods: 0 to 4 weeks, > 4 to 12 weeks, > 12 to 28 weeks, > 28 weeks to 36 weeks, > 36 to end of treatment, and end of treatment to end of the study (including by weekly periods from end of treatment to end of study). For incidence reporting, if a subject reported more than one TEAE 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, TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, end date (if ended), seriousness, severity, action taken regarding the study drug, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided.

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

8.8.2 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, and listings will be provided.

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. A listing of all out-of-range laboratory test results, including assessment of clinical significance, will also be provided.

8.8.3 Vital Signs

The observed vital sign data and change from baseline for each scheduled visit will be summarized with descriptive statistics, and presented in a listing.

8.8.4 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.

8.8.5 Physical Exams

Physical exam findings will be recorded by the sites within medical history or adverse events and otherwise not summarized, with the exception of weight and change from baseline in weight.

8.8.6 Menstrual Diaries

Menstrual diary dates will be used to summarize number and duration of menses.

8.8.7 Hospital Anxiety and Depression Scale

The observed data and change from baseline for the HADS will be summarized with descriptive statistics by scheduled visit. Both the Depression and the Anxiety subscales will be reported.

8.8.8 Epworth Sleepiness Scale

The observed data and change from baseline for the ESS will be summarized with descriptive statistics by scheduled visit.

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, the European Medicines Agency, other Competent Authorities or regulatory agencies with appropriate jurisdiction, 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 will delegate certain aspects of study oversight to Contract Research Organizations (CROs). The specific responsibilities will be detailed in Transfer of Obligations documents.

9.5 Informed Consent

The purpose of the study, the procedures to be carried out, and any potential risks of study participation will be described in non-technical terms in the ICF. After having reviewed and understood the ICF, subjects will be required to read, sign, and date an IRB-approved or EC-approved consent form before any study-specific procedures are carried out. Subjects 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(R2) 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, Investigator Brochure, 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 and ECG data will be recorded in an eCRF system. Data will be entered at the site by the appropriately designated and trained site personnel. All source documents from which eCRF entries are derived should be placed in the subject's medical records. eCRFs will be completed for every subject screened in the study. The investigator/institution should maintain adequate and accurate source documents and trial

records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

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(R2) guideline and the site's data retention policies. These records must be available for inspection by the Sponsor, monitor, and regulatory authorities. Furthermore, the investigators/institutions will permit trial-related monitoring, audits, EC review, and inspections by a competent authority as necessary and provide direct access to source data/documents.

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

9.9 Good Clinical Practice and Ethical Study Conduct

The study procedures outlined in this protocol will be conducted in accordance with applicable ICH Guidelines, including ICH E6(R2): Good Clinical Practice. 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

Examination	**Base-line[1]**	**Week 4 (±7 days)**	**Week 8 (±7 days)**	**Week 12 (±7 days)**	**Week 20 (±7 days)**	**Week 28 (±7 days)**	**Week 36 (±7 days)**	**Week 44 (±7 days)**	**Week 52 (±7 days)**	**ETD[2]**	**Post-drug observation: 3 days (±1 day), and 7, 14, 21, and 28 days (±3 days) after Week 52 Visit**	**Post-drug observation: 35 days (±3 days) after Week 52 Visit**
Informed consent	X											
I/E criteria	X											
Demographics/ Medical History	X											
Physical exam[3]	X[4]	X	X	X[4]	X	X[4]	X	X	X[4]	X[4]		X[4]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Labs[5]	X[1]	X		X		X			X	X		X
Urine pregnancy test[6]	X	X	X	X	X	X	X	X	X	X		X
ECG	X	X			X		X		X	X		X
WI-NRS	X	X	X	X	X	X	X	X	X	X	X	X
IGA PN-S (PN subjects)	X	X	X	X	X	X	X	X	X	X		
DLQI	X				X		X		X	X		
HADS, ESS	X				X		X		X	X	X	X
Photographs (if applicable)	X				X		X		X	X		
Dispense/review menstrual diary (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X
Dispense/collect serlopitant	X	X	X	X	X	X	X	X	X	X		
Review study drug compliance		X	X	X	X	X	X	X				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X

1 Baseline may coincide with the final visit of prior applicable study; Baseline labs do not need to be repeated if completed within prior 14 days

2 Early Treatment Discontinuation

3 Baseline physical exam is complete; all other physical exams are targeted

4 Height/weight at Baseline and weight at Weeks 12, 28, 52 and ETD/post-drug observation 35 days after Week 52

5 Labs are ideally performed in the morning, particularly at visits with endocrine assessments (Baseline, Weeks 12, 28 and 52). Hematology and Chemistry at Baseline, Weeks 4, 12, 28, 52, and ETD/ post-drug observation 35 days after Week 52; Reproductive Endocrinology at Baseline, Weeks 28 and 52 (females under 55 years of age at consent)

6 For females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test). Monthly pregnancy testing can be performed in between visits (and recorded as an Unscheduled visit), and at any time per the investigator's discretion.

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

The list of strong CYP3A4 inhibitors is based on the United States Food and Drug Administration (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

CHECK 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?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Itch										Worst Itch Imaginable

c

APPENDIX D INVESTIGATOR'S GLOBAL ASSESSMENT OF PRURIGO NODULARIS: STAGE

Score	Category	Description: Stage (IGA PN-S)
0	**Clear**	No nodules (0 nodules)
1	**Almost Clear**	Rare, flattened lesions, with no more than 5 dome-shaped palpable nodules (approximately 1-5 nodules)
2	**Mild**	Few, mostly flattened lesions, with small number of dome-shaped palpable nodules (approximately 6-19 nodules)
3	**Moderate**	Many lesions, partially flattened, and dome-shaped palpable nodules (approximately 20-100 nodules)
4	**Severe**	Abundant lesions, majority are dome-shaped palpable nodules (over 100 nodules)

APPENDIX E DERMATOLOGY LIFE QUALITY INDEX

Different language versions may be used.

DERMATOLOGY LIFE QUALITY INDEX

DLQI

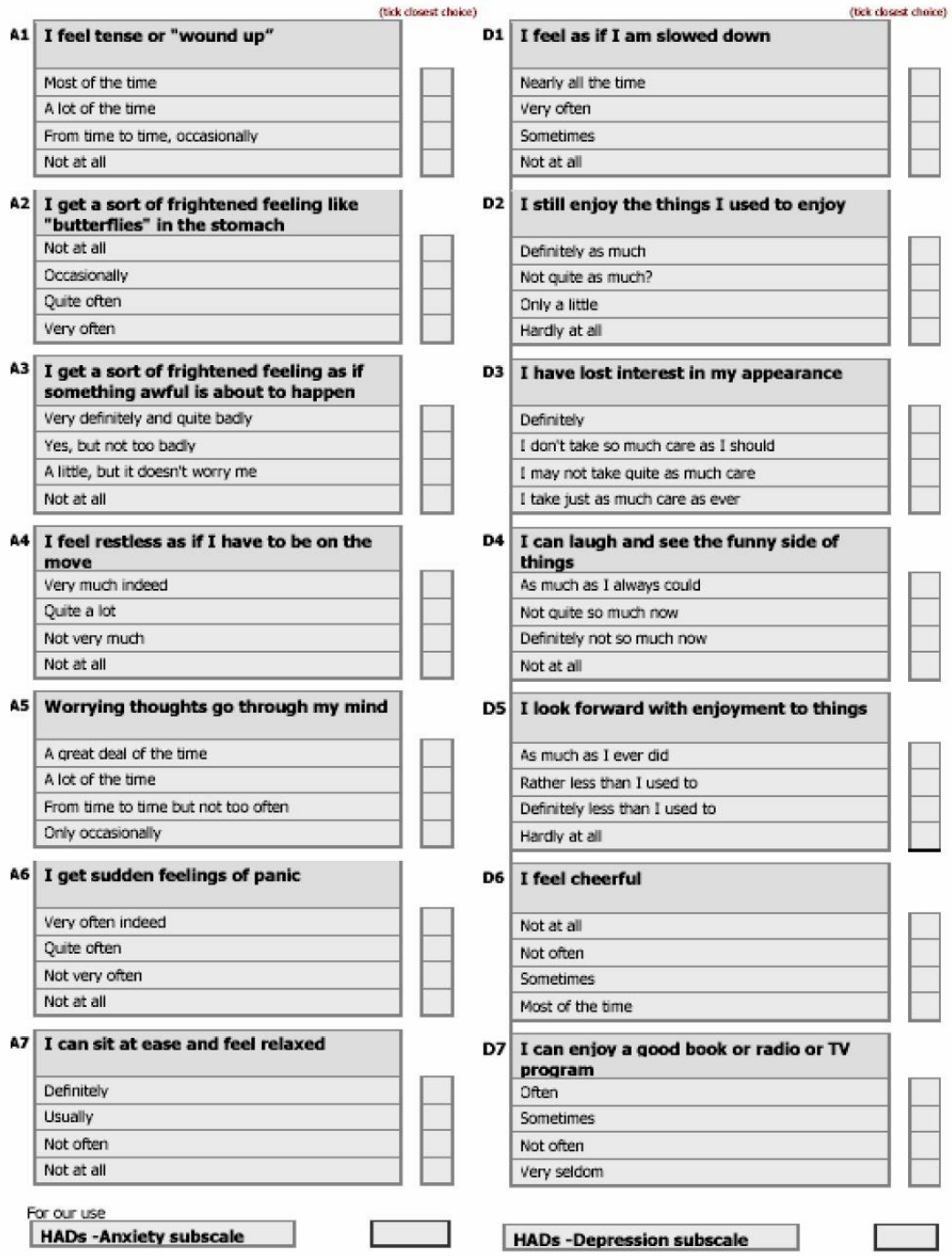
Score: ☐

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

APPENDIX F HOSPITAL ANXIETY AND DEPRESSION SCALE



(tick closest choice)

A1	**I feel tense or "wound up"**	
	Most of the time	
	A lot of the time	
	From time to time, occasionally	
	Not at all	
A2	**I get a sort of frightened feeling like "butterflies" in the stomach**	
	Not at all	
	Occasionally	
	Quite often	
	Very often	
A3	**I get a sort of frightened feeling as if something awful is about to happen**	
	Very definitely and quite badly	
	Yes, but not too badly	
	A little, but it doesn't worry me	
	Not at all	
A4	**I feel restless as if I have to be on the move**	
	Very much indeed	
	Quite a lot	
	Not very much	
	Not at all	
A5	**Worrying thoughts go through my mind**	
	A great deal of the time	
	A lot of the time	
	From time to time but not too often	
	Only occasionally	
A6	**I get sudden feelings of panic**	
	Very often indeed	
	Quite often	
	Not very often	
	Not at all	
A7	**I can sit at ease and feel relaxed**	
	Definitely	
	Usually	
	Not often	
	Not at all	

(tick closest choice)

D1	**I feel as if I am slowed down**	
	Nearly all the time	
	Very often	
	Sometimes	
	Not at all	
D2	**I still enjoy the things I used to enjoy**	
	Definitely as much	
	Not quite as much?	
	Only a little	
	Hardly at all	
D3	**I have lost interest in my appearance**	
	Definitely	
	I don't take so much care as I should	
	I may not take quite as much care	
	I take just as much care as ever	
D4	**I can laugh and see the funny side of things**	
	As much as I always could	
	Not quite so much now	
	Definitely not so much now	
	Not at all	
D5	**I look forward with enjoyment to things**	
	As much as I ever did	
	Rather less than I used to	
	Definitely less than I used to	
	Hardly at all	
D6	**I feel cheerful**	
	Not at all	
	Not often	
	Sometimes	
	Most of the time	
D7	**I can enjoy a good book or radio or TV program**	
	Often	
	Sometimes	
	Not often	
	Very seldom	

To be used under license.

APPENDIX G 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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CLINICAL STUDY PROTOCOL MTI-107

SUMMARY OF CHANGES

Drug Product Name:	Serlopitant
Study Title:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT No.:	2017-004211-40
ClinicalTrials.gov ID:	NCT03540160
Protocol Version:	2.0
Protocol Date:	03 July 2018
Replaces Version/Date:	1.1 / 11 April 2018

The following changes were made to the MTI-107 Clinical Study Protocol from Version 1.1 to Version 2.0.

KEY CHANGES:

Section(s)	Summary of Change	Reason for Change
Protocol Synopsis	Updated consistent with changes to the protocol body.	Ensure consistency between synopsis and protocol body.
1.2.3 Serlopitant in Pruritus-Related Studies	Amended to include language regarding the potential benefit and potential risk for the participating patients as well as the assessment of the ratio of this benefit and risk.	Clarifies the potential benefit and risk for the participating patients.
3.1 Overall Study Design, 6.5 Study Visits	The study post-drug observation period is extended to 5 weeks from 4 weeks.	Allows for the final Post-Drug Observation visit to occur after five terminal elimination half-lives of M2/M2a serlopitant metabolite.
3.3.2 Efficacy Endpoints, 6.1.3 PROMIS Itch Questionnaire, 6.5 Study Visits, 8.7 Efficacy Analyses	Removal of the PROMIS-PIQ associated efficacy endpoints and analyses. Deleted section 6.1.3 and removed PROMIS-PIQ assessments at visits.	The PROMIS-PIQ is not yet validated as a quality of life instrument, thus, this assessment has been removed from the study protocol.
3.3.1 Safety Endpoints, 6.2 Safety Parameters	Added two safety endpoints to measure change from baseline in Hospital Anxiety and Depression Scale (HADS) and the Epworth Sleepiness Scale (ESS) responses.	Safety assessments to evaluate presence and severity of anxiety, depression, and daytime sleepiness while on study drug and during the follow-up period. Evaluation during the follow-up period is intended to support analysis of the study drug's potential for physical dependence.
4.2 Inclusion Criteria	Clarified that for IE criteria #2, participants from TCP-102 study coming into this study or those that have not participated in a prior serlopitant study would need to have WI-NRS score ≥7 in the 24-hour period prior to the Baseline visit.	Defines eligibility criteria with greater specificity.
4.3 Exclusion Criteria	Revised exclusion criterion #2 to identify exclusionary psychiatric diagnoses, without requiring reference to DSM-5 manual.	Defines eligibility criteria with greater specificity.

Section(s)	Summary of Change	Reason for Change
	Revised exclusion criterion #3 to exclude patients with untreated or inadequately treated adrenal or pituitary nodules or disease in addition to untreated or inadequately treated thyroid disease, and history of thyroid malignancy.	
5.3. Dosing Regimen	Study drug may be taken with or without food.	Recent clinical study data has demonstrated that the previous requirement to avoid food for two hours around dosing with serlopitant is unnecessary.
5.6 Study Drug Discontinuation	Revised statement regarding pregnancy to "A female subject desires to become pregnant at the current time, stops contraception or expels her intrauterine device/implant or becomes pregnant", added requirement for study drug discontinuation if "A female subject has new breast findings (e.g. a palpable mass or abnormal mammography, discharge), or has abnormal vaginal discharge or bleeding". Revised statement regarding the best interests of the subject to "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". Revised statement regarding medical conditions that may jeopardize the subject's safety to "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".	Clarification of requirements for study drug discontinuation.
6.1.1 Itch Numeric Rating Scale; 6.1.2	Noted assessment instruments were provided as Appendices.	Clarification only.

Section(s)	Summary of Change	Reason for Change
and 6.1.3 Investigator's Global Assessments; 6.1.4 DLQI		
6.2.2 Physical Examination	Specified that female subjects with targeted breast examinations should have these performed after blood draw for clinical laboratory tests.	Clarification only.
6.2.3 Clinical Laboratory Assessments	Provided instruction on timeframe for laboratory collection, added Endocrine panel, added standard cosyntropin stimulation testing for subjects with low cortisol level. Clarified that pregnancy testing can be performed in between visits and at any time per the investigator's discretion and as required by local authorities. Added optional studies for etiology of PN for participants from TCP-102 study or those that had not participated in a prior clinical study of serlopitant that would be supported through local lab.	Specified endocrinologic laboratory assessments. Clarification only. Support evaluation of underlying disease for subjects with PN for those who did not participate in studies MTI-105 or MTI-106.
6.2.7 Assessment of Potential for Physical Dependence	Provided additional details regarding the assessment of potential for physical dependence via frequent administration of HADS and ESS questionnaires, vital signs, ECG and lab analyses and medical review of all TEAEs reported during this time period.	Specified comprehensive evaluations for physical dependence and withdrawal of study drug.
6.4. Study Visits	Added the requirement for completion of menstrual diaries for female subjects throughout the study. Updated list of procedures for each visit, added additional post-drug observation visits.	Specified request to obtain menstrual data. Clarifications to align with other protocol revisions.
7.1.5 Pregnancies and Contraception Requirement for Females	Clarification of contraceptive requirements including need for highly effective contraception until 5 weeks after last dose of study drug.	Revised section to better align with the "Recommendations related to contraception and pregnancy testing in clinical trials" from the Clinical Trial Facilitation Group (2014).

Section(s)	Summary of Change	Reason for Change
8.8. Safety Analyses	Added weekly analyses of TEAEs during the post-drug observation period. Added HADS and ESS analyses. Added analysis for menstrual diaries.	Supports comprehensive evaluations for physical dependence and withdrawal of study drug. Additional analysis, may correlate with other safety data.
9.2 Study Termination	Added statement that the study may be terminated at the request of the US food and Drug Administration, the European Medicines Agency, other Competent Authorities or regulatory agencies with appropriate jurisdiction, or if the approval to manufacture or to import study drug is revoked by those with jurisdiction.	Clarified termination language to include relevant agencies in Europe and USA.

ADMINISTRATIVE CHANGES:

Section(s)	Summary of Change
Title page	Added protocol version number and release date, added Clinical Trials.gov ID number
Signature Page for Investigator(s)	Added protocol version number and release date, added Clinical Trials.gov ID number
Sponsor Protocol Approval Signature(s)	Added protocol version number, added Clinical Trials.gov ID number
Table of Contents	Updated
List of Abbreviations and Definitions of Terms	Updated for consistency with protocol
Appendix A	Updated tables for consistency with protocol
Appendix B	Updated for consistency with protocol
Appendix C	Added the WI-NRS questionnaire
Appendix D	Added Investigator's Global Assessment of PN Stage scale
Appendix E	Added DLQI
Appendix F	Added Hospital Anxiety and Depression Scale
Appendix G	Added Epworth Sleepiness Scale
Throughout	Updated protocol version in footer; Edited formatting and corrected minor typos and inconsistencies

CLINICAL STUDY PROTOCOL

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT:	2017-004211-40
ClinicalTrials.gov ID:	NCT03540160
Protocol No.:	MTI-107
Protocol Version/Date:	Version 3.0/21 March 2019
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063**,** USA

Confidentiality Statement:

SIGNATURE PAGE FOR INVESTIGATOR(S)

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
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Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063**,** USA

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

_____
Principal Investigator's printed name

_____ _____
Principal Investigator's signature Date (DD-MMM-YYYY)

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

TITLE:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
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Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063, USA

Approved by:

PPD

PROTOCOL SYNOPSIS

Study Title:	An Open-Label Long-Term Safety Study of Serlopitant for the Treatment of Pruritus
Protocol Number:	MTI-107
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Primary objective: • To assess the long-term safety of serlopitant in adults with pruritus associated with prurigo nodularis (PN), atopic dermatitis (AD), or psoriasis. Secondary objectives: • To assess change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS). • To assess change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN. • To assess whether serlopitant produces physical dependence.
Study Design:	Study MTI-107 is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. The study will consist of two periods, for a total study period of approximately 57 weeks: • Treatment period: 52 weeks • Post-drug observation period: 5 weeks During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Standard therapy for the concurrent skin lesions and pruritus may be employed during this study. After completion of the 52-week treatment period, all subjects will enter a 5-week post-drug observation period. Subjects who discontinue treatment early will have post-drug observation visits through 5 weeks after their last dose of serlopitant.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor safety data on a regular basis throughout the study.
Planned Sample Size:	Up to 700 subjects
Study Population:	The study will enroll adults with pruritus associated with PN, AD, or psoriasis. Inclusion Criteria (Subjects must meet the following criteria to be enrolled into the study): 1. Male or female, age 18 years or older at consent. 2. Subject reports pruritus in the 24-hour period prior to enrollment and: a. Has completed a prior applicable clinical study of serlopitant without a serious adverse event (SAE) that was assessed as likely related to the study drug. (For participants from study TCP-102,

	the WI-NRS score must be ≥ 7 in the 24-hour period prior to the Baseline visit.) OR b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and has a WI-NRS score ≥ 7 in the 24-hour period prior to the Baseline visit, and Sponsor has approved enrollment. 3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year) from the time of the Baseline visit until 5 weeks after last dose of study drug. 4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies). 2. Any known major psychiatric diagnosis, such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder, which may confound the assessment of serlopitant safety or efficacy, or interfere with the subject's ability to comply with protocol-mandated activities, within 3 years prior to enrollment. 3. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy; or the presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject. 4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107. 5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment. 6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment. 7. Currently pregnant or breastfeeding or planning to become pregnant during the study.
Study Drug:	Serlopitant 5 mg tablets
Dosage:	Serlopitant: 5 mg once daily orally for 52 weeks
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) and SAEs • Change from baseline in clinical laboratory parameters following study drug exposure • Change from baseline in vital sign and electrocardiogram (ECG) parameters following study drug exposure

	• Change from baseline in the Hospital Anxiety and Depression Scale (HADS) • Change from baseline in the Epworth Sleepiness Scale (ESS) • Assessment of physical dependence following chronic study drug exposure, in the monitored 5-week post-drug discontinuation period
Efficacy Endpoints:	• Change from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52 • Change from baseline in Dermatology Life Quality Index (DLQI) (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52 • Change from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52
Statistical Methods:	All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population. Data will be summarized with descriptive statistics by visit. For continuous variables, the following information will be presented: n, mean, standard deviation, median, minimum and maximum. For categorical variables, counts and percentages will be used. All adverse events (AEs) will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by specified time periods in order to understand the evolution of TEAEs over time. An overview of AEs, which includes subject incidence of TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Summary statistics for actual safety laboratory values and for changes from baseline will be tabulated 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. A listing of all out-of-range laboratory test results, including assessment of clinical significance will also be provided. The observed vital sign data and change from baseline will be summarized with descriptive statistics and presented in a listing. 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. Physical exam findings will be recorded by the sites within medical history or AEs and otherwise not summarized, with the exception of weight, and change from baseline in weight. The WI-NRS, DLQI, and IGA PN-S will be summarized with descriptive statistics by visit. Summary statistics for the HADS and ESS actual values and change from baseline will be presented by scheduled visit.

Study Sites:	Approximately 120 study sites
Expected Duration of Subject's Participation	Approximately 57 weeks: 52 weeks of treatment, and a post-drug observation period of 5 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone, corticotropin
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CYP3A4	Cytochrome P-450 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ESS	Epworth Sleepiness Scale
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
FSH	Follicle-stimulating hormone
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor
NRS	Numeric rating scale
PI	Principal Investigator
PK	Pharmacokinetics
PN	Prurigo nodularis
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus

Pruritus, or itch, is defined as an unpleasant sensation that evokes a desire to scratch (Ikoma 2006). Itch and pain, although closely related, are distinct sensations: itch elicits a scratching response, whereas pain causes a withdrawal response.

Emerging research in neurobiology has greatly expanded the understanding of pruritus signaling. Pruritoceptors (itch-sensory nerve fibers) consist of two distinct classes of nerve fibers: histamine-responsive mechanoinsensitive C-fibers, and histamine-unresponsive mechanosensitive polymodal C and Aδ fibers that are activated by cowhage (highly pruritic spicules from the pods of the cowhage plant *Mucuna pruriens*) (Schmelz 2015). The second class of histamine-unresponsive, cowhage-responsive nerve fibers has been of particular interest in pruritus research, as C-fibers that have a strong and sustained response to histamine comprise only about 20% of the overall mechanoinsensitive C-fiber population (Steinhoff 2006), and a significant proportion of chronic pruritic conditions do not appear to involve histamine-mediated pruritus signaling (Ikoma 2006). Substance P (SP) is a prominent pruritogen (itch mediator) in this histamine-independent pruritus pathway (Chuquilin 2016).

Pruritus stimuli in the skin are transmitted via sensory neurons that have their cell bodies in the dorsal root ganglia (DRG) and are linked to second-order neurons in the spine (Carstens 2016, Luo 2015). Following activation of these DRG sensory neurons, the pruritus signal is transmitted to the second-order spinal neurons primarily by SP, gastrin-releasing peptide, and glutamate in histamine-independent pruritus, and primarily by glutamate in histamine-mediated pruritus (Chuquilin 2016).

Spinal itch neuron projections ascend via the contralateral spinothalamic tract to the thalamus and via the lateral spinoparabrachial tract to the lateral parabrachial nucleus, from which point they activate multiple centers in the somatosensory cortex, the premotor cortex, and the cingulate cortex – areas involved in the sensory processing and motor response (scratching) to the itch signal (Carstens 2016, Chuquilin 2016).

1.1.1 Role of Substance P and the Neurokinin-1 Receptor in Pruritus

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 (NK_1-R), neurokinin-2, and neurokinin-3 receptors (Harrison 2001). The neurokinin-1 receptor, in particular, has been studied in great detail. NK_1-R is the primary receptor for SP in the human body, and is found on multiple cell types, including central and peripheral neurons, keratinocytes, mast cells, and dendritic cells (El-Nour 2006, Ständer 2015).

NK_1-R 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-R 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).

1.2 Serlopitant

1.2.1 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.

1.2.2 Serlopitant Clinical Summary

In humans, serlopitant has been administered to over 1000 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 males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young and elderly subjects. A single loading dose of up to 15 mg followed by 6 to 8 weeks of up to 5 mg daily doses has been well tolerated in adults with chronic pruritus and prurigo nodularis (PN).

Pharmacokinetic data demonstrate good plasma exposures with oral dosing, linear dose-dependent increases in plasma concentration and systemic exposure, a plasma t1/2 appropriate for 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 CCI, M2/M2a CCI, and M3 CCI. 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.

1.2.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

TCP-101 was a double-blind, placebo-controlled, multi-center study that compared serlopitant 0.25 mg, 1 mg, or 5 mg vs. placebo for the treatment of chronic pruritus. A total of 257 adult subjects 18-65 years of age with chronic pruritus were randomized to receive one of the four dose groups in a 1:1:1:1 randomization. Subjects received a loading dose of 3 tablets on Day 1 and thereafter received 1 tablet per day for 6 weeks. The primary efficacy endpoint was itch severity as measured on a Visual Analog Scale (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 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 of the percentage of subjects who were 4-point responders on average VAS at Week 8, 25.0% of placebo subjects and 54.4% of serlopitant subjects were 4-point responders.

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

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

The results of the Phase 2 studies in PN and chronic pruritus, together with the extensive nonclinical and clinical safety data and 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 long-term treatment of pruritus in patients with PN, AD, or psoriasis. The potential benefits of continued clinical study outweigh the potential risks. The data obtained from this long-term study will inform the risks and benefits of long-term exposure (chronic or repeated intermittent use for longer than 6 months). The risk to subjects in this study will be minimized by medical and safety monitoring (see Section 3.4.1).

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

2 STUDY OBJECTIVES

The primary objective of this study is to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis.

The secondary objectives of this study are to assess the change in severity of pruritus in subjects with PN, AD, or psoriasis using the worst-itch numeric rating scale (WI-NRS); to assess the change in severity and extent of PN using the Investigator's Global Assessment of PN Stage (IGA PN-S), for those subjects with PN; and to assess whether serlopitant produces physical dependence.

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, open-label study to assess the long-term safety of serlopitant in adults with pruritus associated with PN, AD, or psoriasis. Eligible subjects who have completed selected studies of serlopitant may be given the opportunity, at the investigator's discretion, to consent to and participate in this open-label study, regardless of their treatment allocation in prior studies. If deemed necessary by Menlo Therapeutics to meet enrollment objectives, eligible subjects who have not participated in a prior serlopitant study may also be enrolled in study MTI-107. Approximately 120 study sites may enroll subjects in this long-term safety study.

This study will consist of two periods, for a total study period of approximately 57 weeks:

- Treatment period: 52 weeks
- Post-drug observation period: 5 weeks

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally (Section 5.3).

Standard therapy for the concurrent skin lesions and pruritus may be employed during this study (Section 5.7.1).

The WI-NRS during a 24-hour recall period will be assessed by the subject at each study visit.

For those subjects with PN, the severity and extent of PN will be assessed at selected visits, using the IGA-PN-S, and photographs of representative areas with PN will be taken at selected visits at a subset of sites.

The Dermatology Life Quality Index (DLQI) will be administered at selected visits.

After completion of the 52-week treatment period, all subjects will enter a 5-week post-drug observation period. Subjects who discontinue treatment early will have a post-drug observation visit through 5 weeks after their last dose of serlopitant. During this monitored discontinuation period, solicited safety evaluations will assess the potential for serlopitant to produce physical dependence.

3.2 Rationale for Study Design and Dose Selection

The current MTI-107 study is designed to confirm the long-term safety of serlopitant for the treatment of pruritus in patients with PN, AD, and psoriasis. The 5 mg dose of serlopitant was selected for this study based on the favorable efficacy, safety, and tolerability profile of serlopitant at this dose level in completed studies.

3.3 Study Endpoints

3.3.1 Safety Endpoints

The safety endpoints are as follows:

- Incidence of TEAEs and SAEs
- Change from baseline in clinical laboratory parameters
- Change from baseline in vital sign and ECG parameters
- Change from baseline in the Hospital Anxiety and Depression Scale (HADS)
- Change from baseline in the Epworth Sleepiness Scale (ESS)
- Assessment of physical dependence following chronic study drug exposure, in the 5-week post-drug discontinuation period.

3.3.2 Efficacy Endpoints

The efficacy endpoints are as follows:

- Change from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Change from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Change from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52

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 safety data on a regular basis throughout the study.

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Up to 700 adult subjects with pruritus associated with PN, AD, or psoriasis will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. Subject reports pruritus in the 24-hour period prior to enrollment and:
    a. Has completed a prior applicable clinical study of serlopitant without an SAE that was assessed as likely related to the study drug (For participants from study TCP-102, the WI-NRS score must be ≥ 7 in the 24-hour period prior to the Baseline visit.)

    OR

    b. Has not participated in a prior clinical study of serlopitant and has a clinical diagnosis of PN, AD, or psoriasis, and has a WI-NRS score ≥ 7 in the 24-hour period prior to the Baseline visit, and Sponsor has approved enrollment.
3. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of <1% per year, refer to Section 7.1.5 for acceptable methods of contraception) from the time of the Baseline visit until 5 weeks after last dose of study drug.
4. Willing and able (has adequate cognitive 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. Presence of malignancy within 5 years prior to enrollment (exception for non-melanoma cutaneous malignancies).
2. Any known major psychiatric diagnosis, such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder, which may confound the assessment of serlopitant safety or efficacy, or interfere with the subject's ability to comply with protocol-mandated activities, within 3 years prior to enrollment.
3. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy; or the presence of any medical condition or disability, that, in the investigator's opinion, could interfere with the assessment of safety in this study or compromise the safety of the subject.
4. Treatment with any investigational therapy within 4 weeks or 5-half-lives prior to enrollment (whichever is longer) or expected participation in another clinical study involving an investigational product or device during the subject's participation in MTI-107.
5. Treatment with other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, fosaprepitant, rolapitant) within 4 weeks prior to enrollment.
6. Treatment with strong cytochrome P450 3A4 inhibitors within 4 weeks prior to enrollment (Appendix B).
7. Currently pregnant or breastfeeding or planning to become pregnant during the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

The study drug in this study is serlopitant 5 mg 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 study drug will be provided in bottles that can be stored at room temperature (59-86°F, 15-30°C).

Each bottle will each contain 18 serlopitant tablets.

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

During the treatment period, subjects will take one serlopitant 5 mg tablet once daily orally. Subjects will be instructed to take all doses from Baseline Visit (Study Day 1) until the Week 52 Visit, once a day. Study drug may be taken with or without food.

Should the study drug be withheld (without intent to discontinue study drug, Section 5.6), the drug may be resumed at the discretion of the investigator, at the same dosing regimen.

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

Each dose of study drug after the first dose must be administered once daily. If a dose is missed, that dose will be considered and documented as a missed dose. Dosing should resume as directed the next day.

5.6 Study Drug Discontinuation

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

- 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
- Baseline serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) (exception may be made for retesting within 28 days of enrollment as approved by the Medical Monitor)
- 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, or withdraws consent from the study
- The subject reports use of a strong CYP3A4 inhibitor (as listed in Appendix B) within 4 weeks of the study visit at which it was reported, initiates any investigational medication, or other NK_1-R antagonist (exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)
- 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 discontinuation due to an AE or pregnancy. Investigators should make every effort to contact the Sponsor or designee before discontinuing study drug, if possible.

Subjects who discontinue study drug prior to completing the treatment period will enter a 5-week follow-up period following the last dose of study drug (Section 6.4.10). Every effort should be made for subjects to complete this follow-up visit after a subject has discontinued from study drug.

5.7 Concomitant and Excluded Therapies

Concomitant therapies include any therapies (including over-the-counter medications) used by a subject from initiation of study drug 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 and routine preventative immunizations.

5.7.1 Excluded Therapies

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

- NK_1-R antagonists (other than study drug, exception may be made for use of approved NK_1-R antagonist for less than 5 continuous days)
- Strong CYP3A4 inhibitors (See Appendix B; exceptions may be made for use within 4 weeks of the study visit at which it was reported)
- Any investigational drug therapy other than serlopitant

Use of any excluded therapies should be reported as soon as possible, and will be recorded as protocol deviations for subjects who receive them. Subjects may be discontinued from the study drug (Section 5.6).

5.8 Assignment to Treatment

Eligible subjects will receive serlopitant 5 mg tablets.

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. Missed doses will be recorded as reported by the subject. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

6 STUDY SCHEDULE AND ASSESSMENTS

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

The Itch NRS is a validated, self-reported instrument for measurement of itch intensity. WI-NRS scores will be captured as per Appendix A. Subjects are asked to rate the intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicate greater itch intensity. In this study, the subject is asked to rate the intensity of their *worst* itch (WI-NRS) during a 24-hour recall period prior to the specified visit; the questionnaire is provided in Appendix C.

6.1.2 Investigator's Global Assessment of PN Stage

The IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 (clear) to 4 (severe), as provided in Appendix D. The IGA PN-S uses clinical characteristics including the number of nodules and their thickness, as guidelines for the overall severity assessment. IGA PN-S scores will be captured as per Appendix A. Each assessment during the study must be done by the principal investigator (PI) or designee. Every effort should be made to ensure that all assessments for a given subject are done by the same individual throughout the study. However, a change in assessor for a given subject, though not ideal, will not be considered a protocol deviation.

6.1.3 Dermatology Life Quality Index

DLQI is a dermatology specific quality of life instrument designed to assess the impact of the skin disease on a subject's quality of life over the prior week. It is a ten-item questionnaire that assesses overall quality of life (QOL) and six aspects that may affect QOL (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and

treatment), and is provided in Appendix E. The DLQI questionnaire will be collected as per Appendix A.

6.1.4 Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as per Appendix A. These areas may include the extensor surfaces of both arms and both legs (overview of both legs, detail of lower legs), and the abdomen and back. The central photography vendor will provide photographic equipment to the sites for use during the study. Detailed instructions will be provided in a Photography Manual.

6.2 Safety Parameters

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

6.2.1 Vital Signs

Vital signs will include measurements of heart rate, 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 as per Appendix A and at unscheduled study visits when clinically indicated. When possible, assessment of vital signs should precede blood draw.

6.2.2 Physical Examination

Physical examinations will be performed as per Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the Baseline visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. The subjects' height and weight will be measured as per Appendix A. For female subjects with targeted breast examinations, 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 as per Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified. When possible, blood draws should follow ECGs and vital sign measurements if they occur on the same visit.

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 (Baseline, Weeks 12, 28, and 52):

- 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, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel
- Endocrine: TSH, free T4, cortisol, corticotropin (adrenocorticotropic hormone, ACTH), prolactin
  - 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.
- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Monthly pregnancy testing can be performed in between visits (and recorded as an Unscheduled visit), and at any time per the investigator's discretion, and as required by local authorities (e.g. in Austria). Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)
- For participants from study TCP-102 or those who had not participated in a prior clinical study of serlopitant, additional optional studies for the etiology of PN (if applicable) will be supported through local procedural and/or laboratory assessments (test kits not supplied by Sponsor). Studies may include, but are not limited to, iron studies (ferritin, serum iron), serum IgE, hepatitis B and C serology, HIV testing, skin biopsy and pathology interpretation, urea breath test for *Helicobacter pylori*, and allergy testing (patch, prick, or blood testing); the investigator should discuss the need for such studies with the medical monitor during the Screening period

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. When possible, ECGs should precede measurement of vital signs and blood draw for clinical laboratory tests. ECGs will be performed as per Appendix A and at unscheduled study visits when clinically indicated. ECGs will be reviewed and reported by a central ECG vendor. The ECG machine and detailed instructions will be provided by the ECG vendor.

6.2.5 Hospital Anxiety and Depression Scale

The HADS is a QOL instrument designed to assess the severity of anxiety and depression over the prior week, developed in a hospital outpatient clinic, but also valid in community

settings and primary care medical practice. The questionnaire takes approximately 2 to 5 minutes to complete, and is provided in Appendix F. The HADS questionnaire will be collected as outlined in Appendix A.

6.2.6 Epworth Sleepiness Scale

The ESS is a QOL instrument intended to measure daytime sleepiness by use of a very short questionnaire. The questionnaire takes approximately 2 to 3 minutes to complete, and is provided in Appendix G. The ESS questionnaire will be collected as outlined in Appendix A.

6.2.7 Assessment of Potential for Physical Dependence

NK_1-R antagonist dependence has not previously been described and therefore a drug class-specific, reliable and sensitive instrument for the assessment of withdrawal symptoms has not been developed. A surrogate assessment tool, such as those developed for opioid or benzodiazepine dependence, is not available.

In order to provide a comprehensive set of assessments for physical dependence and withdrawal symptoms following chronic exposure to the study drug, the HADS and ESS instruments will be administered at baseline and throughout the study period, as well as 3-days and 7-days following the last dose of study drug, and then weekly throughout the 5-week post-study drug observation period. In addition, vital signs will be assessed at each post-study drug observation visit, and an ECG and laboratory analyses will be assessed at the 5-week post-study drug visit. All TEAEs reported during this period will be medically reviewed to assess for possible physical dependence or withdrawal signs or symptoms.

6.3 Subject Flow Diagram

The visit schedule and assessments are summarized in Appendix A.

6.4 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 and 6.2. The timing of each study visit is relative to the day of enrollment (Baseline Visit).

Unscheduled visits may be performed as necessary, and may include procedures or assessments deemed necessary by the investigator and to conduct monthly urine pregnancy testing on females of childbearing potential in between regularly scheduled visits.

Female subjects who report periodic menstruation will be asked to complete a menstrual diary (paper form) throughout the study.

6.4.1 Baseline Visit

The Baseline Visit may coincide with the final visit of the MTI-103, MTI-105, MTI-106, or MTI-109 studies.

The following procedures are to be performed at the Baseline Visit (Day 1):

- Obtain written informed consent prior to any protocol-mandated procedures (must be obtained prior to any other assessments)
- Confirm subject's eligibility based on the inclusion/exclusion
- Collect demographic information (when permitted by regional laws or guidelines: sex, date of birth, race/ethnicity)
- Collect any concomitant medications
- Review and record subject's medical history, including ongoing TEAEs from prior study (if applicable)
  - 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
- Perform complete physical examination (including height and weight)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (exception: participants in MTI-103, MTI-105, MTI-106, and MTI-109 who have had these labs in prior 14 days, in the context of that study)
  - Hematology
  - Chemistry
  - Endocrine
  - Reproductive endocrine labs for females under 55 years of age at consent
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Register Baseline Visit into the Interactive Web Response System (IWRS)

- Dispense study drug
- Provide a menstrual diary to female subjects who report periodic menstruation
- Confirm next scheduled visit date

6.4.2 Week 4 Visit

The Week 4 Visit occurs 28 days (±7 days) after the Baseline Visit. At the Week 4 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.3 Week 8 Visit

The Week 8 Visit occurs 56 days (±7 days) after the Baseline Visit. At the Week 8 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.4 Week 12 Visit

The Week 12 Visit occurs 84 days (±7 days) after the Baseline Visit. At the Week 12 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry

- Endocrine

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.5 Week 20 Visit

The Week 20 Visit occurs 140 days (±7 days) after the Baseline Visit. At the Week 20 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)

- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.6 Week 28 Visit

The Week 28 Visit occurs 196 days (±7 days) after the Baseline Visit. At the Week 28 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
  - Endocrine
  - Reproductive endocrine labs for females under 55 years of age at consent
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.7 Week 36 Visit

The Week 36 Visit occurs 252 days (±7 days) after the Baseline Visit. At the Week 36 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.8 Week 44 Visit

The Week 44 Visit occurs 308 days (±7 days) after the Baseline Visit. At the Week 44 Visit, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)

- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Perform IGA PN-S (for subjects with PN only)
- Collect returned study drug
- Review study drug compliance with re-training as required
- Register visit into the IWRS and utilize IWRS to assign new bottles of study drug
- Confirm next scheduled visit date

6.4.9 Week 52 Visit

The Week 52 Visit occurs 364 days (±7 days) after the Baseline Visit. At the Week 52 Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain ECG
- Obtain vital signs
- Draw blood for clinical laboratory tests
  - Hematology

- Chemistry
- Endocrine
- Reproductive endocrine labs for females under 55 years of age at consent

- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug
- Confirm next scheduled visit date

6.4.10 Early Treatment Discontinuation Visit

The Early Treatment Discontinuation (ETD) Visit occurs within 35 days of last dose for subjects who discontinue serlopitant treatment prior to Week 52.

At the ETD Visit, the following procedures and assessments are to be performed:

- Register visit into the IWRS
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - DLQI
  - HADS
  - ESS
- Perform IGA PN-S (for subjects with PN only)
- Obtain photos (only PN subjects that signed photography consent, only at sites selected for photography)
- Collect returned study drug

6.4.11 Post-Drug Observation Visits

There are six (6) post-drug observation visits.

The Post-Drug Observation Visits occur 3 days (±1 days), 7 days (±3 days), 14 days (±3 days), 21 days (±3 days), 28 days (±3 days), and 35 days (±3 days) after the Week 52 Visit.

At the Post-Drug Observation Visits, the following procedures and assessments are to be performed:

- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess and record any AEs and/or SAEs
- 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
- Perform targeted physical examination, including weight (Only required at post-drug observation visit 35 days after Week 52 visit)
- Obtain ECG (Only required at post-drug observation visit 35 days after Week 52 visit)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test) (Only required at post-drug observation visit 35 days after Week 52 visit)

- Draw blood for clinical laboratory tests (Only required at post-drug observation visit 35 days after Week 52 visit)
  - Hematology
  - Chemistry
- Ask subject to complete WI-NRS
- Ask the subject to complete the following questionnaires:
  - HADS
  - ESS
- Register visit into the IWRS (Only at post-drug observation visit 35 days after Week 52 visit)

6.4.12 Early Termination

Early termination of a subject from the study may occur due to loss to follow-up or withdrawal of consent by the subject. In accordance with legal requirements and International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If 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). Attempts to contact subjects who are suspected of being lost to follow-up 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 or Underlying Pruritic Skin Disease

Pruritus or the underlying pruritic skin disease (PN, AD, or psoriasis) 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. It is important to include a description of the nature of the unexpected worsening when recording the AE or SAE (e.g. new PN lesions in previously uninvolved skin).

7.2 Methods and Timing for Recording and Reporting Adverse Events

7.2.1 Adverse Event Reporting Period

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

AEs and SAEs will be recorded from the first study drug administration through the follow-up visit. After the 5-week 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 Baseline visit procedures but are not enrolled into the study will not have SAEs recorded in the clinical database.

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

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

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

Table 1 Adverse Event Grading

Grade	Severity	Alternate Description[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) v4.03

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 treatment with study drug or participation in the study is not the cause of the AE or SAE.

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

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

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

Please see the 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 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.

8 STATISTICAL METHODS

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

Baseline will be the last recorded value prior to the start of treatment.

A SAP describing all statistical analyses will be written as a separate document.

8.1 Handling of Missing Data and Excluded Therapy Use

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

8.2 Analysis Population

All subjects who receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety population. All analyses will be performed using the safety population.

8.3 Subject Disposition

An accounting of all 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.

8.4 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.5 Concomitant Medications

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

8.6 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.

8.7 Efficacy Analyses

Descriptive statistics will be used to summarize the following:

- Change from baseline in WI-NRS to Weeks 4, 8, 20, 28, 36, 44, and 52
- Change from baseline in DLQI (symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) to Weeks 20, 36 and 52
- Change from baseline in IGA PN-S to Weeks 4, 8, 20, 28, 36, 44, and 52.

Data will be summarized by time point using frequency tabulations or descriptive statistics as appropriate. Observed results, as well as change from baseline will be summarized, as appropriate.

8.8 Safety Analyses

8.8.1 Adverse Events

All AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated in a manner which provides information about the incidence of TEAEs for the entire treatment period as well as by time period in order to understand the evolution of TEAEs over time. Thus, in addition to the TEAE analysis over the entire 12-month treatment time, results will be presented for the following periods: 0 to 4 weeks, > 4 to 12 weeks, > 12 to 28 weeks, > 28 weeks to 36 weeks, > 36 to end of treatment, and end of treatment to end of the study (including by weekly periods from end of treatment to end of study). For incidence reporting, if a subject reported more than one TEAE 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, TEAEs, treatment-related TEAEs, TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, end date (if ended), seriousness, severity, action taken regarding the study drug, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided.

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

8.8.2 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, and listings will be provided.

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. A listing of all out-of-range laboratory test results, including assessment of clinical significance, will also be provided.

8.8.3 Vital Signs

The observed vital sign data and change from baseline for each scheduled visit will be summarized with descriptive statistics, and presented in a listing.

8.8.4 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.

8.8.5 Physical Exams

Physical exam findings will be recorded by the sites within medical history or adverse events and otherwise not summarized, with the exception of weight and change from baseline in weight.

8.8.6 Menstrual Diaries

Menstrual diary dates will be used to summarize number and duration of menses.

8.8.7 Hospital Anxiety and Depression Scale

The observed data and change from baseline for the HADS will be summarized with descriptive statistics by scheduled visit. Both the Depression and the Anxiety subscales will be reported.

8.8.8 Epworth Sleepiness Scale

The observed data and change from baseline for the ESS will be summarized with descriptive statistics by scheduled visit.

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, the European Medicines Agency, other Competent Authorities or regulatory agencies with appropriate jurisdiction, 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 will delegate certain aspects of study oversight to Contract Research Organizations (CROs). The specific responsibilities will be detailed in Transfer of Obligations documents.

9.5 Informed Consent

The purpose of the study, the procedures to be carried out, and any potential risks of study participation will be described in non-technical terms in the ICF. After having reviewed and understood the ICF, subjects will be required to read, sign, and date an IRB-approved or EC-approved consent form before any study-specific procedures are carried out. Subjects 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(R2) 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, Investigator Brochure, 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 and ECG data will be recorded in an eCRF system. Data will be entered at the site by the appropriately designated and trained site personnel. All source documents from which eCRF entries are derived should be placed in the subject's medical records. eCRFs will be completed for every subject screened in the study. The investigator/institution should maintain adequate and accurate source documents and trial

records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

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(R2) guideline and the site's data retention policies. These records must be available for inspection by the Sponsor, monitor, and regulatory authorities. Furthermore, the investigators/institutions will permit trial-related monitoring, audits, EC review, and inspections by a competent authority as necessary and provide direct access to source data/documents.

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

9.9 Good Clinical Practice and Ethical Study Conduct

The study procedures outlined in this protocol will be conducted in accordance with applicable ICH Guidelines, including ICH E6(R2): Good Clinical Practice. 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

Examination	Base-line[1]	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 20 (±7 days)	Week 28 (±7 days)	Week 36 (±7 days)	Week 44 (±7 days)	Week 52 (±7 days)	ETD[2]	Post-drug observation: 3 days (±1 day), and 7, 14, 21, and 28 days (±3 days) after Week 52 Visit	Post-drug observation: 35 days (±3 days) after Week 52 Visit
Informed consent	X											
I/E criteria	X											
Demographics/ Medical History	X											
Physical exam[3]	X[4]	X	X	X[4]	X	X[4]	X	X	X[4]	X[4]		X[4]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Labs[5]	X[1]	X		X		X			X	X		X
Urine pregnancy test[6]	X	X	X	X	X	X	X	X	X	X		X
ECG	X	X			X		X		X	X		X
WI-NRS	X	X	X	X	X	X	X	X	X	X	X	X
IGA PN-S (PN subjects)	X	X	X	X	X	X	X	X	X	X		
DLQI	X				X		X		X	X		
HADS, ESS	X				X		X		X	X	X	X
Photographs (if applicable)	X				X		X		X	X		
Dispense/review menstrual diary (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X
Dispense/collect serlopitant	X	X	X	X	X	X	X	X	X	X		
Review study drug compliance		X	X	X	X	X	X	X				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X

1 Baseline may coincide with the final visit of prior applicable study; Baseline labs do not need to be repeated if completed within prior 14 days

2 Early Treatment Discontinuation

3 Baseline physical exam is complete; all other physical exams are targeted

4 Height/weight at Baseline and weight at Weeks 12, 28, 52 and ETD/post-drug observation 35 days after Week 52

5 Labs are ideally performed in the morning, particularly at visits with endocrine assessments (Baseline, Weeks 12, 28 and 52). Hematology and Chemistry at Baseline, Weeks 4, 12, 28, 52, and ETD/ post-drug observation 35 days after Week 52; Reproductive Endocrinology at Baseline, Weeks 28 and 52 (females under 55 years of age at consent)

6 For females of childbearing potential (with positive or equivocal results to be confirmed by a serum pregnancy test). Monthly pregnancy testing can be performed in between visits (and recorded as an Unscheduled visit), and at any time per the investigator's discretion.

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

The list of strong CYP3A4 inhibitors is based on the United States Food and Drug Administration (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

CHECK 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?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

No Itch

Worst Itch Imaginable

c

APPENDIX D INVESTIGATOR'S GLOBAL ASSESSMENT OF PRURIGO NODULARIS: STAGE

Score	Category	Description: Stage (IGA PN-S)
0	**Clear**	No nodules (0 nodules)
1	**Almost Clear**	Rare, flattened lesions, with no more than 5 dome-shaped palpable nodules (approximately 1-5 nodules)
2	**Mild**	Few, mostly flattened lesions, with small number of dome-shaped palpable nodules (approximately 6-19 nodules)
3	**Moderate**	Many lesions, partially flattened, and dome-shaped palpable nodules (approximately 20-100 nodules)
4	**Severe**	Abundant lesions, majority are dome-shaped palpable nodules (over 100 nodules)

APPENDIX E DERMATOLOGY LIFE QUALITY INDEX

Different language versions may be used.

DERMATOLOGY LIFE QUALITY INDEX

DLQI

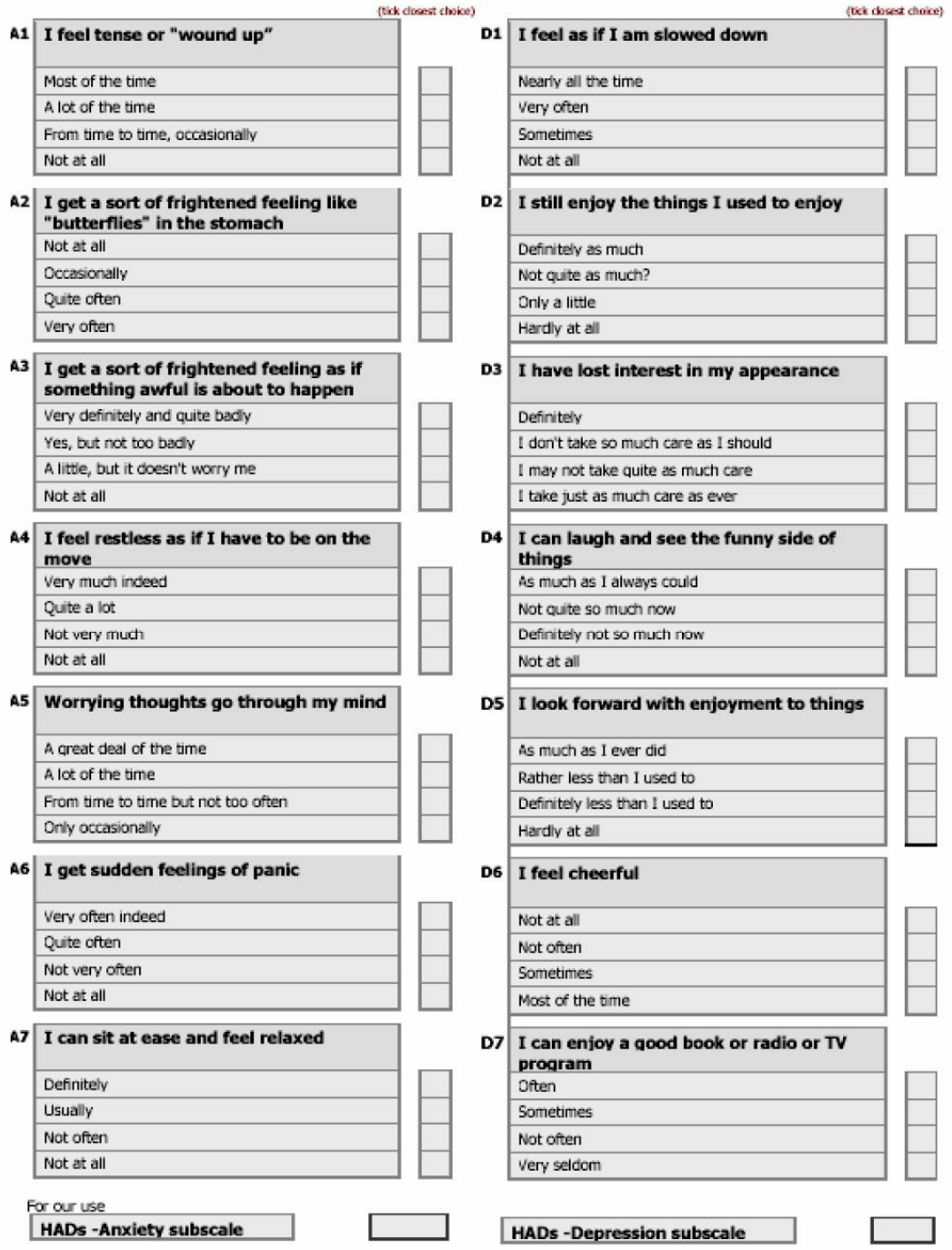
Score: ☐

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

APPENDIX F HOSPITAL ANXIETY AND DEPRESSION SCALE



(tick closest choice)

A1	**I feel tense or "wound up"**	
	Most of the time	☐
	A lot of the time	☐
	From time to time, occasionally	☐
	Not at all	☐
A2	**I get a sort of frightened feeling like "butterflies" in the stomach**	
	Not at all	☐
	Occasionally	☐
	Quite often	☐
	Very often	☐
A3	**I get a sort of frightened feeling as if something awful is about to happen**	
	Very definitely and quite badly	☐
	Yes, but not too badly	☐
	A little, but it doesn't worry me	☐
	Not at all	☐
A4	**I feel restless as if I have to be on the move**	
	Very much indeed	☐
	Quite a lot	☐
	Not very much	☐
	Not at all	☐
A5	**Worrying thoughts go through my mind**	
	A great deal of the time	☐
	A lot of the time	☐
	From time to time but not too often	☐
	Only occasionally	☐
A6	**I get sudden feelings of panic**	
	Very often indeed	☐
	Quite often	☐
	Not very often	☐
	Not at all	☐
A7	**I can sit at ease and feel relaxed**	
	Definitely	☐
	Usually	☐
	Not often	☐
	Not at all	☐

(tick closest choice)

D1	**I feel as if I am slowed down**	
	Nearly all the time	☐
	Very often	☐
	Sometimes	☐
	Not at all	☐
D2	**I still enjoy the things I used to enjoy**	
	Definitely as much	☐
	Not quite as much?	☐
	Only a little	☐
	Hardly at all	☐
D3	**I have lost interest in my appearance**	
	Definitely	☐
	I don't take so much care as I should	☐
	I may not take quite as much care	☐
	I take just as much care as ever	☐
D4	**I can laugh and see the funny side of things**	
	As much as I always could	☐
	Not quite so much now	☐
	Definitely not so much now	☐
	Not at all	☐
D5	**I look forward with enjoyment to things**	
	As much as I ever did	☐
	Rather less than I used to	☐
	Definitely less than I used to	☐
	Hardly at all	☐
D6	**I feel cheerful**	
	Not at all	☐
	Not often	☐
	Sometimes	☐
	Most of the time	☐
D7	**I can enjoy a good book or radio or TV program**	
	Often	☐
	Sometimes	☐
	Not often	☐
	Very seldom	☐

For our use

HADs -Anxiety subscale ☐ **HADs -Depression subscale** ☐

To be used under license.

APPENDIX G 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

ESS - United States/English - Version of 19 Jan 18 - Mapi.
ID037309 / ESS_AU1.0_eng-US2.doc

CLINICAL STUDY PROTOCOL MTI-107

SUMMARY OF CHANGES

Drug Product Name:	Serlopitant
Study Title:	AN OPEN-LABEL LONG-TERM SAFETY STUDY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS
IND No.:	117780
EudraCT No.:	2017-004211-40
ClinicalTrials.gov ID:	NCT03540160
Protocol Version:	3.0
Protocol Date:	21 March 2019
Replaces Version/Date:	2.0 / 03 July 2018

The following changes were made to the MTI-107 Clinical Study Protocol from Version 2.0 to Version 3.0.

KEY CHANGES:

Section(s)	Summary of Change	Reason for Change
Synopsis	Changed number of patients from 400 to 700	**Permits enrollment of additional eligible patients**
4.1 Study Population	Changed number of patients from 400 to 700	**Permits enrollment of additional eligible patients**

ADMINISTRATIVE CHANGES:

Section(s)	Summary of Change
Title page	Updated protocol version number and release date
Signature Page for Investigator(s)	Updated protocol version number and release date
Sponsor Protocol Approval Signature(s)	Updated protocol version number
Throughout	Updated protocol version in footer; Edited formatting and corrected minor typos and inconsistencies