- **Protocol number:** MTI-106.
- **Document title:** A randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with prurigo nodularis.
- **Version number:** Protocol Version 4.
- **Date of the document:** 16 December 2019.
- **NCT number:** NCT03677401

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

The following protocols under which subjects were enrolled and summaries of changes are provided:

- Protocol Version 2.1 (02 July 2018)
- Summary of Changes, Version 2.1 to 3.0
- Protocol Version 3.0 (21 March 2019)
- Summary of Changes, Version 3.0 to 4.0
- Protocol Version 4.0 (16 December 2019)

CLINICAL STUDY PROTOCOL

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
IND No.:	117780
Eudra CT:	2017-004210-25
ClinicalTrials.gov ID:	[Placeholder]
Protocol No.:	MTI-106
Protocol Version/Date:	Version 2.1/02 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 PRINCIPAL INVESTIGATOR(S)

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
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I have read the protocol and agree to conduct this study in accordance with the protocol, all relevant laws and regulations in force at the time, International Conference on Harmonisation Guidelines for Good Clinical Practices, and the Declaration of Helsinki.

_____
Principal Investigator's printed name

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

SIGNATURE PAGE FOR COORDINATING INVESTIGATOR

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

Coordinating Investigator's printed name

_____ _____

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

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

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

Approved by:

PPD

PPD

PPD

03 JUL 2018

Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Pruritus in Adults With Prurigo Nodularis
Protocol Number:	MTI-106
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Efficacy objective: To assess the efficacy of serlopitant for the treatment of pruritus in adults with prurigo nodularis. Safety objective: To assess the safety and tolerability of repeated oral doses of serlopitant in adults with prurigo nodularis.
Study Design:	This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with prurigo nodularis (PN). Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 3- or 5-week follow-up period. The study will consist of three periods, for a total study period of 15 to 19 weeks: • Screening period: 2-4 weeks • Treatment period: 10 weeks • Follow-up period: 3 or 5 weeks During the screening period, all subjects will undergo eligibility evaluation and will be assessed for chronic pruritic conditions frequently associated with PN. Subjects who present with idiopathic PN at screening may require additional assessments as deemed necessary by the investigator (e.g. endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis, skin biopsy for subjects with signs or symptoms of bullous pemphigoid or cutaneous T-cell lymphoma, urea breath test for *Helicobacter pylori*, or allergy testing). All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of electronic diary (eDiary) screening data. Subjects who require a screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit. Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study. At the Baseline visit (Day 1), eligible subjects will be randomly assigned to receive study drug (serlopitant 5 mg or placebo). Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Day 1). Starting on Day 2, subjects will take one tablet per day. Study drug may be taken with or without food.

	The primary efficacy endpoint will be assessed at Week 10 of treatment. Subjects who complete the 10-week treatment period and required follow-up period may be given the opportunity to enroll in a one-year open-label safety study with daily oral doses of serlopitant 5 mg.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor blinded safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 200 subjects will be randomized.
Study Population:	The study will consist of adult subjects with pruritus associated with PN. Inclusion Criteria (Subjects must meet the following criteria to be randomized into the study): 1. Male or female, age 18 years or older at consent. 2. A diagnosis of PN, defined by the presence of at least ten pruriginous nodules secondary to chronic pruritus present on at least two different body surface areas (e.g. both arms, one arm and one leg, one arm and the anterior trunk, or anterior and posterior trunk). 3. The worst pruritus is identified to be within the areas of the PN lesions. 4. Subject has idiopathic PN OR the subject has an identified pruritic condition associated with the PN and has persistent pruritus despite at least 6 weeks of optimized and stable treatment of the underlying condition prior to the Baseline visit, and is willing to continue the treatment during the study. 5. Worst-Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the 24-hour period prior to the Screening visit. 6. Average weekly WI-NRS score ≥ 6.5 in each of the 2 weeks (14 days) immediately prior to Baseline visit, as recorded in the eDiary. 7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last dose of study drug. 8. Willing and able (as demonstrated by a ≥ 70% eDiary completion rate in the two weeks prior to Baseline visit) to complete daily eDiary entries within a consistent timeframe for the duration of the study. 9. 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. Prior treatment with serlopitant. 2. Active pruritic skin disease, other than PN, within 6 months prior to randomization (with the exception of acute dermatoses such as contact dermatitis, sunburn, viral exanthem, which have been resolved for longer than 4 weeks). 3. Treatment with any of the following therapies within 4 weeks prior to randomization.

	a. Other neurokinin-1 receptor antagonists (e.g., aprepitant, fosaprepitant, rolapitant). b. Systemic or topical immunosuppressive/immunomodulatory therapies (including but not limited to corticosteroids, phosphodiesterase-4 inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, interferon-gamma, thalidomide, or phototherapy). c. Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists (e.g. naloxone, naltrexone)). d. Strong cytochrome-P 3A4 inhibitors. e. Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn. 4. Treatment with topical anti-pruritic therapies (e.g., menthol, camphor, pramoxine, capsaicin) within 2 weeks prior to randomization. 5. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer. 6. Treatment with any investigational therapy within 4 weeks (8 weeks for investigational biologic therapies) or 5 half-lives prior to randomization, whichever is longer. 7. Serum creatinine, total bilirubin, alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal during screening. 8. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy. 9. History of malignancy within 5 years prior to randomization, with the exception of actinic keratosis, completely treated and non-metastatic cutaneous basal cell carcinoma or squamous cell carcinoma of the skin. 10. 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 randomization. 11. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt. 12. Documented history of parasitic infection, including skin parasites such as scabies, within 8 weeks prior to randomization. 13. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject. 14. History of hypersensitivity to serlopitant or any of its components. 15. Currently pregnant or breastfeeding female subject. 16. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated

	assessments (e.g. extended international travel) during the subject's participation in the study.
Study Drug:	Serlopitant 5 mg oral tablets and matching placebo.
Dosage:	Serlopitant: 5 mg once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period. Matching placebo: Once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period.
Primary Efficacy Endpoint:	The primary efficacy endpoint is the WI-NRS 4-point responder rate at Week 10.
Secondary Efficacy Endpoints:	The key secondary efficacy endpoints are as follows: • WI-NRS 4-point responder rate at Week 4 • Change from baseline in WI-NRS to Day 7 • Change from baseline in WI-NRS to Day 3 • Change from baseline in Dermatology Life Quality Index (DLQI) to Week 10 Additional secondary efficacy endpoints are as follows: • Change from baseline in WI-NRS to other timepoints • WI-NRS 4-point responder rate at Week 2 • WI-NRS 3-point responder rate at Weeks 2, 4 and 10 • Change from baseline in Investigator's Global Assessment of PN Activity to Weeks 2, 4 and 10 • Change from baseline in Investigator's Global Assessment of PN Stage to Weeks 2, 4 and 10
Safety Endpoints:	Safety endpoints are as follows: • Incidence of treatment-emergent adverse events and serious adverse events (SAEs) • Changes from baseline in clinical laboratory parameters following study drug exposure • Changes from baseline in vital sign and electrocardiogram (ECG) parameters following study drug exposure • Changes from baseline in the Hospital Anxiety and Depression Scale (HADS) • Changes from baseline in the Epworth Sleepiness Scale (ESS)
Decision Rule and Sample Size:	This study will use a 5% two-sided alpha level. Hierarchical testing in which statistical significance for the key secondary efficacy endpoints requires statistical significance for the primary endpoint. The target sample size of 200 randomized and dosed subjects (100 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. Two hundred subjects results in 90% power assuming a placebo responder rate of CCI% and serlopitant rate of CCI%.
Statistical Methods:	Efficacy analyses will be based upon an intent-to-treat philosophy. The primary

	efficacy population will be the Intent-to-Treat (ITT) population that will include all randomized subjects who were dispensed study drug. Analyses performed on the Per Protocol population will be considered supportive. Subjects will be analyzed within the treatment group to which they are randomized. Efficacy Analyses: The primary efficacy endpoint is a binary variable taking on values of responder or non-responder. Subjects will be considered a responder if they have at least a 4-point reduction in WI-NRS between baseline and Week 10. Missing data imputation will be used for subjects who fail to complete the eDiary at Week 10, unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. The primary endpoint will be summarized with descriptive statistics by treatment group and study week. The difference in the primary efficacy outcome measure between treatment groups will be tested using a Cochran Mantel Haenszel test controlling for the stratification factors. Testing of the key secondary efficacy endpoints will also be employed.
	Safety Analyses: The incidence of all adverse events (AEs) and treatment-related AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. An overview of AEs, which includes subject incidence of AEs, treatment-related AEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Clinical safety laboratory values will be measured by a central laboratory. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Graphs of laboratory values over time will also be produced. Subjects with clinical laboratory values outside of the normal reference range at any post-baseline assessment will be summarized. Shifts from baseline laboratory values will be tabulated. The overall ECG assessment (abnormal or normal) will be summarized along with a summary of how many subjects developed a post treatment abnormal result. Summary statistics for the HADS and ESS actual values and change from baseline will be presented by scheduled visit.
Study Sites:	Approximately 50 study sites.
Expected Duration of Subject's Participation	15-19 weeks: 2-4 weeks of screening, 10 weeks of treatment, and a follow-up period of 3 or 5 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone, corticotropin
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CMH	Cochran Mantel Haenszel test
CNS	Central Nervous System
CRO	Contract Research Organization
CYP3A4	Cytochrome-P 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ESS	Epworth Sleepiness Scale
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAART	Highly active antiretroviral therapy
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-A	Investigator's Global Assessment of Prurigo Nodularis Activity
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
LFC	Liquid filled capsule
LH	Luteinizing hormone
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor

NOAEL	No observed adverse effect level
NRS	Numeric Rating Scale
PET	Positron Emission Tomography
PI	Principal Investigator
PD	Pharmacodynamics
PDE-4	Phosphodiesterase-4
PK	Pharmacokinetics
PN	Prurigo nodularis
PP	Per Protocol
QOL	Quality of life
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus in Prurigo Nodularis

Prurigo nodularis (PN) is a distinctive and easily diagnosable chronic skin condition characterized by the presence of multiple highly pruritic and often symmetrically distributed nodules and papules on the skin (Jorizzo 1981). The nodules and papules in PN can range in size from approximately 0.5 to 3.0 cm and often appear hyperkeratotic, sometimes crateriform, in appearance. Plaques are occasionally present, and the lesions of PN frequently exhibit other features secondary to prolonged and severe scratching behavior, such as post-inflammatory hyperpigmentation, erosion, ulceration, crusting, and bleeding (Zeidler 2016).

PN, a long-term reaction to the chronic scratching and picking of patients with chronic pruritus (Zeidler 2016), is a skin condition seen predominantly in older adults, with median prevalence age in the 50s and 60s and a slight female preponderance (Iking 2013, Tan 2014, Ständer 2013). In one patient population survey, pediatric patients accounted for <2% of the total population, with the youngest patient 11.9 years of age (Iking 2013). Although only limited epidemiology data for PN have been published, a claims-based analysis commissioned by Menlo Therapeutics suggest that the United States (US) prevalence may be in the range of ~ 355,000 affected individuals. Based on a quantitative survey of 73 dermatologists conducted in parallel with the claims-based analysis, approximately 23% of patients with PN have an underlying atopy-related condition, while over 50% are considered to be idiopathic (Navigant 2017). The median duration of disease burden has been reported to be 6-7 years (Iking 2013, Tan 2014, Schuhknecht 2011).

The dominant symptom in PN is an intense and chronic pruritus that is associated with a high degree of patient burden and restricted quality of life (QOL) (Zeidler 2016). As measured by global scales of pruritus intensity (numeric rating scale (NRS) and visual analog scale (VAS)), median levels of pruritus intensity have been reported to be 7-8 points (Iking 2013, Tan 2014, Schuhknecht 2011). The pruritus experienced in PN can often prevent patients from adequately performing their daily activities (Vaidya 2008), and patients with PN have been found to suffer from greater rates of depression and anxiety than control groups in numerous studies (Jorgensen 2016, Rowland Payne 1985, Dazzi 2011).

1.2 Conditions Associated With Prurigo Nodularis

As PN is considered to be a disease induced by chronic pruritus and ongoing scratching activity, a variety of chronic pruritic conditions have been identified as potential underlying etiologies for the pruritus, including atopic dermatitis (AD), other inflammatory or bullous skin diseases, chronic renal failure, human immunodeficiency virus (HIV) infection, hepatitis C infection, and multifactorial disease (i.e. two or more co-existent conditions associated with chronic pruritus) (Fostini 2013, Lee 2005). The mechanisms linking chronic pruritus to the development of PN are not clear, as only a subset of patients with chronic pruritus develop PN, and over half of patients with PN have no underlying etiology identified. Even when specific underlying conditions are identified, management of these condition(s) does not usually result in resolution of PN signs or symptoms, nor can all underlying conditions be treated. For example, PN has been observed in patients with HIV adequately managed with

highly active antiretroviral therapy (HAART) (Zancanaro 2006), in patients with intractable cholestatic pruritus (Bergasa 2011), in patients with inactive hepatitis (Halvorsen 2015), and commonly in patients with renal failure despite hemodialysis therapy (Goeksel 2013). These data point to a high level of unmet medical need in the overall PN population, as the majority of patients with PN either have no underlying condition identified that can be treated, or treatment of the underlying condition is inadequate to control their PN (Wallengren 2004).

1.3 Current Treatment Options for Prurigo Nodularis

Treatment of PN remains a challenging and extremely frustrating experience for both patients and physicians. In the majority of cases, responses are limited and unsatisfactory, and once the cycle of pruritus-excoriation-pruritus begins, it is difficult to stop. Identification and treatment of underlying chronic pruritic conditions is often the first step in management of PN. If this does not result in resolution of the pruritus, or if no underlying condition is identified, treatment specifically for PN and its associated pruritus is implemented.

First-line pruritus therapies, including topical agents such as topical corticosteroids and calcineurin inhibitors, often provide inadequate response (Saco 2015) and the therapeutic ladder for PN involves systemic agents with progressively riskier safety profiles. These include naltrexone, gabapentin, mirtazapine, phototherapy, intravenous immunoglobulin (IVIG), powerful immunosuppressants such as methotrexate and cyclosporine, and thalidomide (Ständer 2015b, Spring 2014, Feldmeyer 2012, Lim 2016). None of these therapies are indicated for the treatment of PN, and their usage is often based on limited evidence, such as case reports or small open-label studies.

1.4 Substance P and the Neurokinin-1 Receptor

Repeated itching, scratching, and picking over long time periods serve as the pathophysiological basis for the development of PN. Although different underlying disease states may be responsible for the chronic pruritus, the distinctive and easily recognizable features of PN point to a common final pathway resulting in this unique clinical presentation.

Immunohistochemical staining studies of PN biopsies have demonstrated that nerve fibers immunoreactive for Substance P (SP) are found in increased numbers in lesional skin compared to non-lesional skin or controls (Abadía Molina 1992), suggesting a role for SP signaling in PN. These findings are consistent with the robust body of evidence indicating the key role of SP signaling through its primary receptor, the neurokinin-1 receptor (NK_1-R), in the transmission of itch across multiple disease states (Santini 2012, Akiyama 2015, Crowe 1994, El-Nour 2006, Lotts 2014, Hon 2007, Ward 2004, Slattery 2011).

SP is an undecapeptide that belongs to the tachykinin family of neuropeptides, a group that also includes neurokinin A and neurokinin B (Hökfelt 2001). SP has been implicated in a number of biological functions, both physiological and pathophysiological, including pruritus perception, vomiting reflex, pain perception, and immunomodulatory responses (Lotts 2014, Andoh 1998, Steinhoff 2014). The biological actions of SP are mediated by tachykinin receptors, which consist of seven hydrophobic transmembrane domains coupled to G-proteins. Three tachykinin receptors have been identified: the neurokinin-1, neurokinin-2,

and neurokinin-3 receptors (Harrison 2001). The NK_1-R 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, include central and peripheral neurons, keratinocytes, and mast cells.

NK_1-R stimulation has been shown to be an important pathway for pruritus perception (Ständer 2015a). 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).

1.5 Serlopitant

1.5.1 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.

1.5.2 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 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 [redacted] M2/M2a [redacted], and M3 [redacted]. 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.

1.5.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

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

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

squares mean difference compared to placebo was 5.8 mm, 13.2 mm, and 14.2 mm for serlopitant 0.25 mg, 1 mg, and 5 mg, respectively.

The frequency of 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.

Potential Risks and Benefits: 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 treatment of pruritus in patients with PN. The potential benefits of continued clinical study outweigh the potential risks.

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

2 STUDY OBJECTIVES

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

The safety objective of this study is to assess the safety and tolerability of repeated oral doses of serlopitant in adults with PN.

3 STUDY DESIGN

3.1 Overall Study Design

This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with PN. The study will be conducted at approximately 50 study sites. Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 3 or 5-week follow-up period. The required follow-up period is defined as a minimum of 3 weeks for those subjects who will enroll in the one-year open-label safety study (MTI-107) on the date of the follow-up visit, and as 5 weeks for those subjects who will not be enrolled in the one-year open-label safety study of serlopitant. Should a subject present for the follow-up visit prior to 5 weeks after the last dose of study drug and be excluded from participation in the one-year study for any reason, the subject will be required to return at 5 weeks after the last dose of study drug for a complete follow-up visit.

This study will consist of three periods, for a total study period of 15-19 weeks:

- Screening period: 2-4 weeks
- Treatment period: 10 weeks
- Follow-up period: 3 or 5 weeks

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

During the screening period, all subjects will undergo eligibility evaluation and will be assessed for chronic pruritic conditions frequently associated with PN. Subjects who present with idiopathic PN at screening may require additional assessments as deemed necessary by the investigator (e.g. endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis, skin biopsy for subjects with signs or symptoms of bullous pemphigoid or cutaneous T-cell lymphoma, urea breath test for *Helicobacter pylori*, or allergy testing).

All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of electronic diary (eDiary) screening data. Subjects who require screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred following discussion with the medical monitor should more than 31 days be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition).

Screening procedures may be repeated (i.e., the subject may be rescreened) following discussion with the medical monitor should the subject have had difficulty complying with eDiary assessments, require further training in the assessments, or have other relevant needs that may delay enrollment in the study but are not expected to impact safety or efficacy assessments.

Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study.

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

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

Subjects who complete the 10-week treatment period and required follow-up period may be given the opportunity to enroll in a one-year open-label safety study (MTI-107) with daily oral doses of serlopitant 5 mg.

3.2 Rationale for Study Design and Dose Selection

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

patients with chronic pruritus, serlopitant 5 mg and 1 mg taken daily for 6 weeks were superior to placebo for the reduction of pruritus, in both the overall study population and the subgroup of subjects with an atopic diathesis.

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

The current MTI-106 study is designed to confirm the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in patients with PN. 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. Over 250 subjects have been exposed to serlopitant at doses of 5 mg tablet-equivalent daily for at least 6 weeks, and ~ 40 subjects have been exposed up to one year. Human CNS PET RO data for serlopitant in healthy young males (Study P002) demonstrated that a serlopitant 5 mg LFC once daily dose is likely to achieve ~ 94% NK_1 RO at steady state.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

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

3.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- WI-NRS 4-point responder rate at Week 4
- Change from baseline in WI-NRS to Day 7
- Change from baseline in WI-NRS to Day 3
- Change from baseline in Dermatology Life Quality Index (DLQI) to Week 10

3.3.3 Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints are as follows:

- Change from baseline in WI-NRS to other timepoints
- WI-NRS 4-point responder rate at Week 2
- WI-NRS 3-point responder rate at Weeks 2, 4 and 10
- Change from baseline in Investigator's Global Assessment of PN Activity (IGA PN-A) to Weeks 2, 4 and 10
- Change from baseline in Investigator's Global Assessment of PN Stage (IGA PN-S) to Weeks 2, 4 and 10

3.3.4 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs and SAEs
- Change from baseline in clinical laboratory parameters following study drug exposure
- Change from baseline in vital sign and 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)

3.4 Safety Review

3.4.1 Safety Monitoring Team

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

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 200 adult subjects with pruritus associated with PN will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. A diagnosis of PN, defined by the presence of at least ten pruriginous nodules secondary to chronic pruritus present on at least two different body surface areas (e.g. both arms, one arm and one leg, one arm and the anterior trunk, or anterior and posterior trunk).
3. The worst pruritus is identified to be within the areas of the PN lesions.
4. Subject has idiopathic PN OR the subject has an identified pruritic condition associated with the PN and has persistent pruritus despite at least 6 weeks of optimized and stable

treatment of the underlying condition prior to the Baseline visit, and is willing to continue the treatment during the study. Please refer to Section 5.7.1.

5. WI-NRS score ≥ 7 in the 24-hour period prior to the Screening visit.
6. Average weekly WI-NRS score ≥ 6.5 in each of the 2 weeks (14 days) immediately prior to Baseline visit, as recorded in the eDiary.
7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last dose of study drug. Please refer to Section 7.1.5 for acceptable methods of contraception.
8. Willing and able (as demonstrated by a ≥ 70% eDiary completion rate in the two weeks prior to Baseline visit) to complete daily eDiary entries within a consistent timeframe for the duration of the study.
9. 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. Prior treatment with serlopitant.
2. Active pruritic skin disease, other than PN, within 6 months prior to randomization (with the exception of acute dermatoses such as contact dermatitis, sunburn, viral exanthem, which have been resolved for longer than 4 weeks). Please refer to Section 5.7.1.
3. Treatment with any of the following therapies within 4 weeks prior to randomization.
    a. Other NK_1-R antagonists (e.g., aprepitant, fosaprepitant, rolapitant).
    b. Systemic or topical immunosuppressive/immunomodulatory therapies (including but not limited to corticosteroids, phosphodiesterase-4 (PDE-4) inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, interferon-gamma, thalidomide, or phototherapy).
    c. Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists (e.g. naloxone, naltrexone)).
    d. Strong CYP3A4 inhibitors (see Appendix B).
    e. Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn.
4. Treatment with topical anti-pruritic therapies (e.g., menthol, camphor, pramoxine, capsaicin) within 2 weeks prior to randomization (see Section 5.7.2).

5. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer.
6. Treatment with any investigational therapy within 4 weeks (8 weeks for investigational biologic therapies) or 5 half-lives prior to randomization, whichever is longer.
7. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) during screening.
8. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease or history of thyroid malignancy.
9. History of malignancy within 5 years prior to randomization, with the exception of actinic keratosis, completely treated and non-metastatic cutaneous basal cell carcinoma or squamous cell carcinoma of the skin.
10. 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 randomization.
11. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt.
12. Documented history of parasitic infection, including skin parasites such as scabies, within 8 weeks prior to randomization.
13. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject.
14. History of hypersensitivity to serlopitant or any of its components.
15. Currently pregnant or breastfeeding female subject.
16. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g. extended international travel) during the subject's participation in the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

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

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

The tablets will be supplied in bottles, with 18 tablets per bottle. One bottle will be issued via Interactive Web Response System (IWRS) at baseline and at Weeks 2 and 4, and two bottles will be issued via IWRS at Week 6. A total of 5 bottles will be dispensed to subjects completing 10 weeks of study drug treatment.

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

5.2 Labeling and Study Drug Accountability

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

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

5.3 Dosing Regimen

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

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

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

5.6 Study Drug Discontinuation

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

- A female subject desires to become pregnant at the current time, stops contraception or expels her intrauterine device/implant, or becomes pregnant
- A female subject has new breast findings (e.g. a palpable mass or abnormal mammography, discharge), or has abnormal vaginal discharge or bleeding
- The subject decides to discontinue study drug treatment, or withdraws consent from the study
- The subject receives a strong CYP3A4 inhibitor (See Appendix B)
- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion; this may include the development of persistently (2 successive occasions) abnormal thyroid function tests (TSH >10, or TSH > 6 with low free T4; TSH <0.1, or TSH < 0.35 with high free T4); abnormal morning prolactin, cortisol, or corticotropin levels; or signs and symptoms of adrenal insufficiency

- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion, including evidence that the subject does not meet inclusion/exclusion criteria intended primarily for safety reasons, or a persistent lack of adherence to study procedures

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

Subjects who discontinue treatment with study drug prior to completing the treatment period will enter a 5-week follow-up period following the last dose of study drug in addition to a Follow-up visit (see Section 3.1, Section 6.5.10). Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued from study drug.

5.7 Prior, Concomitant, and Excluded Therapies

Prior therapies (including over-the-counter medications) used to treat the signs and symptoms of PN within the prior 2 years will be recorded for each subject at the Baseline visit.

Concomitant therapies include any therapies (including over-the-counter medications and bland emollients) used by a subject from initiation of study drug treatment through the follow-up period. A record of all medications used will be maintained for each subject throughout the study. Reported information will include a description of the type of drug, treatment period, dosing regimen, the route of administration, and drug indication. The use of any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements, emollient use, and routine preventative immunizations.

5.7.1 Allowed Therapies and Treatment Goals for Underlying Conditions

Treatment of an underlying, treatable chronic pruritic condition is allowed, if stable for at least 6 weeks prior to the Baseline visit, and continued throughout the treatment period.

Treatment of the underlying systemic pruritic condition should be optimized per standard of care and treatment goals must be tailored based on age, sex, and concurrent health status and drug tolerance. While resolution of metabolic or endocrine disorders or eradication of an underlying infection may not always be feasible, every effort should be made to ensure the condition is well controlled, to prevent or reduce exacerbations and to prevent limitation on the activities of daily living. When applicable, laboratory evidence of control should be obtained. For example, if renal insufficiency is implicated as causal for pruritus, treatment would be expected to have meaningfully reduced the creatinine (compared to that at the time of diagnosis) and to maintain the creatinine at < 2.5 the ULN; control of diabetes is supported by a hemoglobin-A1c of < 7.5%; control of thyroid disease is supported by normalization of the thyroid stimulating hormone (TSH) or by a TSH within 1.5 times the ULN in elderly patients; iron deficiency is corrected with a serum iron within 0.8 times the lower limit of normal; eradication of *Helicobacter pylori* infection generally requires a negative urea breath

test and fecal antigen test and endoscopy; and the viral load should be undetectable if viral infections such as hepatitis B or hepatitis C, or HIV were previously diagnosed. Any previously active skin disease is considered to be well controlled if it is globally considered clear or almost clear (permissible to have post-inflammatory pigmentation, fine scale, faint pink erythema, barely perceptible induration/papulation, and no oozing or crusting).

Use of gentle cleansers and bland emollients (including those with urea) is encouraged for all subjects. If bland emollient use is elected, it must be initiated at least 2 weeks (14 days) prior to Baseline visit, and continued throughout the treatment period.

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

Leukotriene inhibitors will be permitted for treatment of conditions other than PN (e.g. asthma).

5.7.2 Excluded Therapies

Initiation or use of topical therapy with corticosteroids, calcineurin inhibitors, calcipotriene, PDE-4 inhibitors is not permitted within 4 weeks prior to the Baseline visit or throughout the treatment period, but such therapy may be initiated during the follow-up period if needed.

Initiation of bland emollient is not permitted within 2 weeks (14 days) prior to Baseline visit or throughout the treatment period, but such therapy may be initiated during the follow-up period if needed.

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

- NK_1-R antagonists (other than study drug)
- Systemic immunosuppressive/ immunomodulatory therapies (including but not limited to systemic corticosteroids, PDE-4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, thalidomide, interferon-gamma, or phototherapy)
- Biologic therapies (other than therapies such as insulins, vaccines)
- Strong CYP3A4 inhibitors (See Appendix B)
- Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn
- Any investigational therapy

The following therapies and activities are excluded from the Screening visit through the treatment period, and use is discouraged, though permitted, through the follow-up period:

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

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

5.7.3 Rescue Therapies

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

5.8 Assignment to Treatment

5.8.1 Randomization

Eligible subjects will be randomized to receive serlopitant 5 mg or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by the subject's reported WI-NRS score for the 1-week period prior to the Baseline visit (6.5 to < 9, 9 to 10).

An IWRS will be used to perform the randomization.

5.8.2 Blinding

This study will be conducted as a double-blind study with the treatment assignment concealed from the subjects, the investigators and their staff, the Sponsor, and any designees of the Sponsor as required. The placebo will be formulated to be indistinguishable from the active study product. Study materials will be packaged and issued in a manner designed to maintain the blind for subjects and all study personnel involved in the direction and execution of study procedures, study assessments, and collection of data. The randomization code for each subject will be available to the sites for use only in an emergency situation. For details of the procedure for unblinding of individual subjects in cases of emergency see Section 7.6.

5.9 Treatment Compliance

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

6 STUDY SCHEDULE AND ASSESSMENTS

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

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

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

6.1.2 Investigator's Global Assessment of PN Activity

The IGA PN-A is an instrument used to assess the overall activity 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-A uses clinical characteristics of excoriations, crusting, and/or bleeding as guidelines for the overall activity assessment. The number of pruriginous lesions should not be considered for this assessment. IGA PN-A scores will be captured as outlined in 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 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 of number of nodules and their thickness as guidelines for the overall severity assessment. IGA-PN-S scores will be captured as outlined in Appendix A. Each assessment during the study must be done by the 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.

6.1.4 Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI) is a dermatology specific QOL instrument designed to assess the impact of the skin disease on a subject's QOL over the prior week. It is a ten-item questionnaire that assesses overall 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 outlined in Appendix A.

6.1.5 PN Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as outlined in 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. The PI and designees will be trained on the use of the camera and the appropriate lighting and positioning of the representative area with PN involvement. Detailed instructions will be provided in the 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 as outlined in Appendix A.

6.2.1 Vital Signs

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

6.2.2 Physical Examination

Physical examinations, including height and weight measurements, will be performed as outlined in Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the screening visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. 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 outlined in Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified.

Detailed instructions regarding sample collection, preparation, and shipment can be found in the laboratory manual. Laboratory assessments will include the following, and are ideally performed in the morning, particularly at visits with endocrine assessments (Screening, Week 10, Follow-up):

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, uric acid, total protein, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel
- Iron studies: ferritin, serum iron
- Serology: hepatitis B and C serology, HIV
- Serum IgE
- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Endocrine: TSH, free T4, cortisol, corticotropin (adrenocorticotropic hormone, ACTH), prolactin
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)
- Optional study provided in lab test kits for use at Screening only: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis

- Additional optional studies will be supported through local procedural and/or laboratory assessments, including, but not limited to, 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.
- Standard cosyntropin stimulation testing should be performed on subjects with low cortisol level (i.e. < 3.0 mcg/dL); the investigator should discuss low cortisol (and relevant low corticotropin) results with the medical monitor.

6.2.4 Electrocardiogram

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

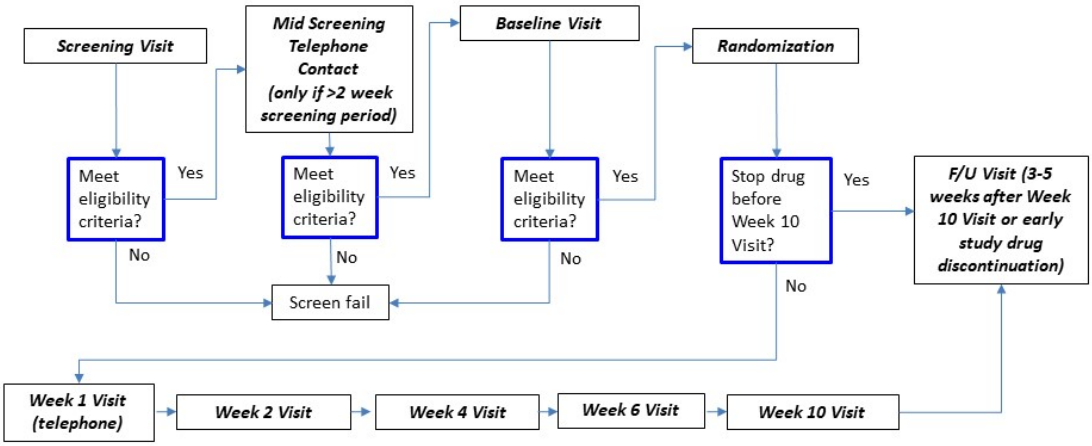
6.3 Pharmacokinetic Measurements

Sparse PK sampling will involve collecting one PK sample at each of the Week 2, Week 4, and Week 10 visits as outlined in Appendix A. The date and time of dosing prior to PK sample collection and date and time of PK sample collection will be collected. The plasma concentrations of serlopitant and metabolites will be determined and data used for population PK analysis. Detailed instructions regarding PK sample collection, preparation, and shipment can be found in the laboratory manual.

6.4 Subject Flow Diagram

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

Figure 1 Subject Flow Diagram



6.5 Study Visits

The following sections describe the procedures and assessments to be performed at each study visit. Details of each procedure and assessment can be found in Sections 6.1, 6.2, and 6.3. The timing of each study visit is relative to the day of randomization (Baseline).

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

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

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

6.5.1 Screening Period

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

All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of eDiary screening data. Subjects who require screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred following discussion with the medical monitor should more than 31 days be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition).

Screening procedures may be repeated (i.e., the subject may be rescreened) following discussion with the medical monitor should the subject have had difficulty complying with eDiary assessments, require further training in the WI-NRS assessments, or have other relevant needs that may delay enrollment in the study but are not expected to impact safety or efficacy assessments.

6.5.2 Screening Visit

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

- Obtain written informed consent prior to any protocol-mandated procedures, including the stopping of any excluded therapies
- Collect demographic information (sex, date of birth, race, ethnicity)
- Ask subject to complete the WI-NRS scale on paper
- Register Screening visit into the IWRS
- Obtain ECG
- Obtain vital signs
- Review subject's medical history (including prior medications)
  - Record only significant/relevant medical history, to include the onset date of PN (as specifically as known) and presence of an underlying condition (if any)
  - Designate the primary and any concurrent medical conditions that are identified as pruritic conditions underlying the PN
  - 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) and confirm clinical diagnosis of PN
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
  - Serology
  - Serum IgE
  - Iron studies
  - Optional: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis
  - Optional: additional assessments (refer to Section 6.2.3)
- Review subject's tentative eligibility according to the Inclusion/Exclusion criteria
  - The results of all screening evaluations, including laboratory and ECG results, must be reviewed for clinical significance by the PI or designee, and may require further evaluation, prior to randomization of the subject on Baseline visit
- Schedule the Baseline visit and all future study visits to ensure subject's availability and visit compliance with the protocol visit windows
- Provide a menstrual diary to female subjects who report periodic menstruation
- Provide eDiary with instructions
- Confirm next scheduled visit

6.5.3 Mid-Screening Telephone Contact (for subjects longer than 14 days in Screening)

During this telephone contact the following procedures are to be performed:

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

6.5.4 Baseline Visit

The Baseline visit occurs between 14 to 31 days after the screening visit, depending on the required washout period following discontinuation of excluded therapies. Eligibility must be confirmed prior to randomization. At the Baseline visit, the following procedures and assessments are to be performed, preferably in the order shown below:

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Assess and record any changes in the subject's medical history
  - Female subjects should be queried regarding history of, or current, breast masses or abnormal discharge, and history of mammography (if applicable), and history of abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess AE's and record SAEs caused by protocol-mandated interventions
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential and confirm the subject has a negative urine pregnancy test result prior to randomization (with positive or equivocal results confirmed by a serum pregnancy test)
- Confirm subject's eligibility based on the inclusion/exclusion criteria (to include review of eDiary compliance for eligibility)
- Randomize subject in IWRS if eligibility confirmed
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Dispense study drug; subjects will take loading dose of 3 tablets while on site
- Review eDiary for compliance, re-train subject as needed
- Assess and record any post-dose AEs and SAEs
- Confirm next scheduled visit

6.5.5 Week 1 Telephone Contact Visit

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

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

6.5.6 Week 2 Visit

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

- 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
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Collect returned study drug

- Utilize IWRS to assign new bottle of study drug
- Confirm next scheduled visit date

6.5.7 Week 4 Visit

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

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign new bottle of study drug
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.8 Week 6 Visit

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

- 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
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Perform targeted physical examination, including weight
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign new bottle of study drug
- Review eDiary for compliance, re-train subject as needed
- Confirm next scheduled visit

6.5.9 Week 10 Visit

The Week 10 visit occurs 70 days (± 7 days) after the Baseline visit. At the Week 10 visit, the following procedures and assessments are to be performed:

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Collect returned study drug
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Review eDiary for compliance, inform subject to continue entering WI-NRS score until Follow-up visit
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.10 Follow-up Visit

The required Follow-up visit occurs 21 or 35 (+7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early. The required follow-up period is defined as a minimum of 3 weeks for those subjects who will enroll in the one-year open-label safety study on the date of the follow-up visit, and as 5 weeks for those subjects who will not be enrolled in the one-year open-label safety study of serlopitant. Should a subject present for the follow-up visit prior to 5 weeks after the last dose of study drug and be excluded from participation in the one-year study for any reason, the subject will be required to return at 5 weeks after the last dose of study drug for a complete follow-up visit.

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

- Register visit into the IWRS
- Ask the subject to complete the HADS and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain vital signs

- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Obtain ECG
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
- Assess and record any AEs and SAEs
- Collect eDiary device, review eDiary for compliance

6.5.11 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) –GCP guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If provided, the reason (adverse event, study burden, lack of efficacy, other) a subject withdrew consent will be recorded in the electronic Case Report Form (eCRF). The PI or site staff must make every effort to contact subjects who are suspected of being lost to follow-up. Attempts to contact such subjects must be documented in the subject's source documents.

7 ASSESSMENT OF SAFETY

7.1 Definitions

7.1.1 Adverse Event

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

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

7.1.2 Serious Adverse Event

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

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

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

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

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

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

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

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

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

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

7.1.4 Deaths

Any deaths that occur from the time of informed consent to the follow-up visit, regardless of attribution, must be reported within 24 hours of investigator's awareness of the death. See Safety Form Completion Instructions for complete instructions.

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

7.1.5 Pregnancies and Contraception Requirements for Females

For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal, unless permanently surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female.

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

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

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

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

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

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

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

7.1.6 Worsening of Pruritus or PN

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

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

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

All AEs entered into the eCRF will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 study drug treatment or participation in the study is not the cause of the AE or SAE.

7.4 Reporting Serious Adverse Events to the Sponsor and Institutional Review Board or Ethics Committee

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

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

Please see the Safety Form Report Completion Instructions for safety reporting instructions.

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

7.5 Reporting Serious Adverse Events to Regulatory Authorities and Study Investigators

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

7.6 Emergency Unblinding

Emergency unblinding is available 24 hours per day/7 days per week and will be performed via IVRS. An investigator may unblind a subject's treatment assignment only when knowledge of the investigational product is essential for the welfare of a subject. There is no specific antidote for serlopitant and usual supportive medical management is recommended in the case of a medical emergency.

8 STATISTICAL METHODS

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. Endpoints will be summarized with descriptive statistics by treatment group and visit. For continuous variables, the following information will be presented: n (number of subjects), mean, standard deviation, median, minimum and maximum. For categorical variables counts and percentages will be used. Summary statistics for imputed efficacy data will be reported based upon imputed data.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Subjects who withdrew from the study due to a lack of efficacy, or used an excluded therapy to treat worsening of pruritus or PN, will be defined as non-responder.

As one sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). As a second sensitivity analysis, a repeated measures model will be used on observed data. Additionally, a tipping point analysis will be done as a sensitivity analysis for the primary endpoint.

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

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

8.1 Decision Rule and Sample Size

This study will use a 5% two-sided alpha level. While the alpha level is two-sided, clinically relevant results require a serlopitant benefit. Statistical significance for the key secondary efficacy endpoints requires statistical significance for the primary efficacy endpoint (i.e. stepdown testing from primary to key secondary endpoints). The key secondary efficacy endpoints will be tested in order starting with the Week 4 WI-NRS 4-point responder rate, then change from baseline to Day 7, and then Day 3, and finally the change from baseline to Week 10 in DLQI.

The target sample size of 200 randomized and dosed subjects (100 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. A sample size of two hundred subjects results in 90% power assuming a placebo responder rate of [redacted]% and serlopitant rate of [redacted]%.

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

8.2 Handling of Missing Data

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

The primary method of handling missing efficacy data will be MCMC multiple imputation. Subjects who withdrew from the study due to a lack of efficacy, or used an excluded therapy to treat worsening of pruritus or PN, will be defined as non-responder. Imputation will be conducted within each treatment group independently, so the pattern of missing observations in one treatment group cannot influence missing value estimations in another. For each imputation process, 25 imputations will be performed.

If a subject fails to complete their eDiary for the week prior to Week 10, the primary endpoint (WI-NRS) data will be missing, unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. If the Week 10 value is missing for any other reason, the change from baseline value will be based on imputed data. Missing Week 10 WI-NRS values from which the 4-point responder status is derived will be estimated by MCMC.

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

1. Using the daily eDiary data, calculate Baseline and Week 2 through Week 10 values by averaging available values. If any values are available, these will be used i.e. a minimum of 1 observation is required to compute a week's average.

2. From step 1, create a dataset for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing WI-NRS values in each dataset will be filled in using the MCMC method to generate 25 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset.

Syntax:

```
proc mi data=datain out=dataout seed=&seed. Nimpute=25 <options>;
  where trtpn=(TRT);   /* Note TRT = [1, 2]; depending on treatment group */;
  mcmc chain=single;
  var baseline d2 d3 d4 d5 d6 d7 week2 week3 week4 week5 week6 week7 week8
week9 week10;
run;
```

3. From each complete dataset, the dichotomous responder rate will be determined. Each complete dataset will be analyzed as specified for the particular analysis.

Missing Week 10 DLQI data will be derived for the analysis using the method of MCMC multiple imputation. The following steps will be followed:

1. DLQI for Week 10 will be calculated as per scoring instructions.

2. From step 1, create a dataset for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing values in each dataset will be filled in using the MCMC method to generate 25 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset.

Syntax:

```
proc mi data=datain out=dataout seed=&seed. Nimpute=25 <options>;
  where trtpn=(TRT);   /* Note TRT = [1, 2]; depending on treatment group */;
  mcmc chain=single;
  var baseline week4 week10;
run;
```

3. Each complete dataset will be analyzed as specified for the particular analysis.

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

A total of 4 random seeds will be needed to impute missing data. Those random seeds have been pre-specified by using a random number generator:

8.3 Analysis Populations

The primary efficacy population will be the Intent-to-Treat (ITT) and will include all randomized subjects who were dispensed study drug. Subjects will be analyzed within the treatment group to which they are randomized.

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

The Per Protocol (PP) population will include all subjects in the safety population who complete the Week 10 evaluations without any significant protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). Analyses performed on the Per Protocol population will be considered supportive. The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Receives a strong CYP3A4 inhibitor (See Appendix B);
- Receives an excluded medication for treatment of pruritus or PN;
- Have not been compliant with the dosing regimen (i.e. subjects must comply with 80–120% of the expected dosage of study medication during participation in the study);
- Out of visit window at the Week 10 visit by ±7 days

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

8.4 Subject Disposition

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

8.5 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.6 Prior and Concomitant Medications

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

Prior therapies (including over-the-counter medications) used to treat the signs and symptoms of PN within the prior 2 years will be reported. Prior medications will be summarized by ATC level and preferred drug name and listed.

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

8.7 Treatment Compliance and Extent of Exposure

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

8.8 Efficacy Analyses

All efficacy endpoints will be summarized within the ITT and PP populations using descriptive statistics by time point and treatment. Results including averaged imputed values will be summarized at Baseline, Week 2 (if available), 4, 10 and Follow-up, and the change from baseline for these measures will be summarized at Week 2, 4, 10 and Follow-up. The WI-NRS and change from baseline will also be presented for each study day.

8.8.1 Primary Efficacy

The difference in the primary efficacy outcome measure (WI-NRS 4-point responder rate at Week 10) will be tested using a CMH test controlling for the 'as randomized' stratification factors. Conceptually the hypotheses being tested are:

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

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

8.8.2 Key Secondary Efficacy

The differences between treatment groups for the key secondary efficacy endpoint, Week 4 WI-NRS 4-point responder rate, will be the CMH test identical to the one used for the primary endpoint.

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

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

The preceding tests are to be conducted for the ITT population and the PP populations.

8.8.3 Additional Secondary Efficacy

Additional secondary efficacy endpoints will include analyses analogous to the primary and key secondary efficacy analyses. Additional secondary efficacy endpoints which may be drawn from the primary and key secondary imputations (including all WI-NRS endpoints) will be analyzed using the imputed data. Additional secondary efficacy endpoints otherwise will be analyzed using available data. P-values will be included for descriptive purposes only.

8.9 Sensitivity Analyses

8.9.1 Last Observation Carried Forward

In the first set of sensitivity analysis, missing values will be imputed using LOCF. Data will be imputed using LOCF unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. Each primary and key secondary endpoint will be analyzed as it was using the multiply imputed data.

8.9.2 Repeated Measures Analysis

The second set of sensitivity analyses will be performed on observed data.

The dichotomized primary/key secondary efficacy endpoints will each be analyzed with a repeated measures logistic regression model (generalized estimating equations), with the dichotomized endpoint as the dependent variable and treatment, stratification factor and visit (Weeks 2, 4, 10) as independent factors

The remaining key secondary efficacy variables will be analyzed with a repeated measures ANCOVA, with treatment, stratification factor and applicable timepoints as independent factors and a covariate of baseline value.

8.9.3 Tipping Point Analysis

A sensitivity analysis for the handling of missing data for the primary efficacy endpoint will be carried out using a tipping point analysis.

8.10 Safety Analyses

8.10.1 Adverse Events

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

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

8.10.2 Clinical Safety Laboratory Results

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

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

8.10.3 Vital Signs

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

8.10.4 Electrocardiograms

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

8.10.5 Physical Exams

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

8.10.6 Menstrual Diaries

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

8.10.7 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.

8.10.8 Epworth Sleepiness Scale

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

8.11 Population Pharmacokinetics Analysis

The plasma concentrations of serlopitant and metabolites will be combined with the data from other serlopitant clinical studies for population PK analysis with PK endpoint of individual model parameter estimates and covariates identification. A specific population PK data analysis plan will be developed that will outline the detailed approach to data handling,

model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques. The population PK analysis report will not be a part of the clinical study report.

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 guideline. The protocol, ICF, other written subject information, and any proposed study advertising material must be submitted to the IRB or EC for written approval. IRB or EC approval of these documents will be provided to the investigator. The study will not start until the IRB or EC has granted its approval of the study materials and procedures.

Protocol amendments will be submitted to the IRB or EC as explained in Section 9.1. SAE information will be submitted to the IRB or EC as explained in Section 7.4.

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

9.7 Disclosure and Confidentiality

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

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

9.8 Records and Electronic Case Report Forms

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

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

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

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

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

9.9 Good Clinical Practices and Ethical Study Conduct

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

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

9.10 End of Study Notification

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

9.11 Publication of Results

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

9.12 Final Report

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

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APPENDIX A SCHEDULE OF ACTIVITIES AND ASSESSMENTS

Table 2 Schedule of Visit Activities

Examination	Screening	Mid-Screening[TC]	Baseline[1]	Week 1[TC] (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 10 (± 7 days)	F/U[2]	Early Treatment Discontinuation
Demographics	X									
Informed consent	X									
WI-NRS[3]	X	X	X	X	X	X	X	X		
DLQI			X			X		X		X
HADS, ESS			X			X		X	X	X
ECG	X				X	X		X	X	X
Vital signs	X		X		X	X	X	X	X	X
Medical history (and prior medications)	X	X	X							
Physical exam[4]	X		X		X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X
Labs[5]	X				X			X	X	X
Urine pregnancy test[6]	X		X			X	X	X	X	X
PK blood draw					X	X		X		
Review of I/E criteria	X	X	X							
IGA PN-A and IGA PN-S			X		X	X		X	X	X
Photography (selected sites)			X					X	X	X
Dispense/review menstrual diary (if applicable)	X		X		X	X	X	X	X	X
Dispense/collect eDiary	X								X	X
eDiary review/compliance[7]		X	X	X	X	X	X	X	X	
Dispense and/or collect study drug			X		X	X	X	X		X
Review study drug compliance					X	X	X	X		
AEs/SAEs[8]	X	X	X	X	X	X	X	X	X	X

[TC]Telephone Contact: The Mid-Screening telephone contact should only occur for subjects who require a washout longer than 2 weeks, at least 15 days prior to the scheduled Baseline visit.

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

[2]The Follow-up (F/U) visit occurs 21-35 days (+ 7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early.

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

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

[5]Labs are ideally performed in the morning, particularly at visits with endocrine assessments (including Reproductive Endocrinology for females under 55 at age of consent) at Screening, Week 10 and Follow Up. Iron Studies, serum IgE and Serology labs are done only at Screening visit; endomysial antibody test and other optional studies only performed at Screening;

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

[7]See Table 3 for eDiary assessments

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

Table 3 Schedule of eDiary Assessments

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

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

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

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

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

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

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

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

APPENDIX C WORST ITCH NUMERIC RATING SCALE QUESTIONNAIRE

NRS for Itch Intensity

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

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

Score	Category	Description: Activity (IGA PN-A)
0	**Clear**	No nodules have excoriations or crusts
1	**Almost Clear**	Very small proportion of nodules have excoriations or crusts (up to approximately 10% of all nodules)
2	**Mild**	Minority of nodules have excoriations or crusts (approximately 11- 25% of all nodules)
3	**Moderate**	Many nodules have excoriations or crusts (approximately 26- 75% of all nodules)
4	**Severe**	Majority of nodules have excoriations or crusts (approximately 76-100% of all nodules)

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

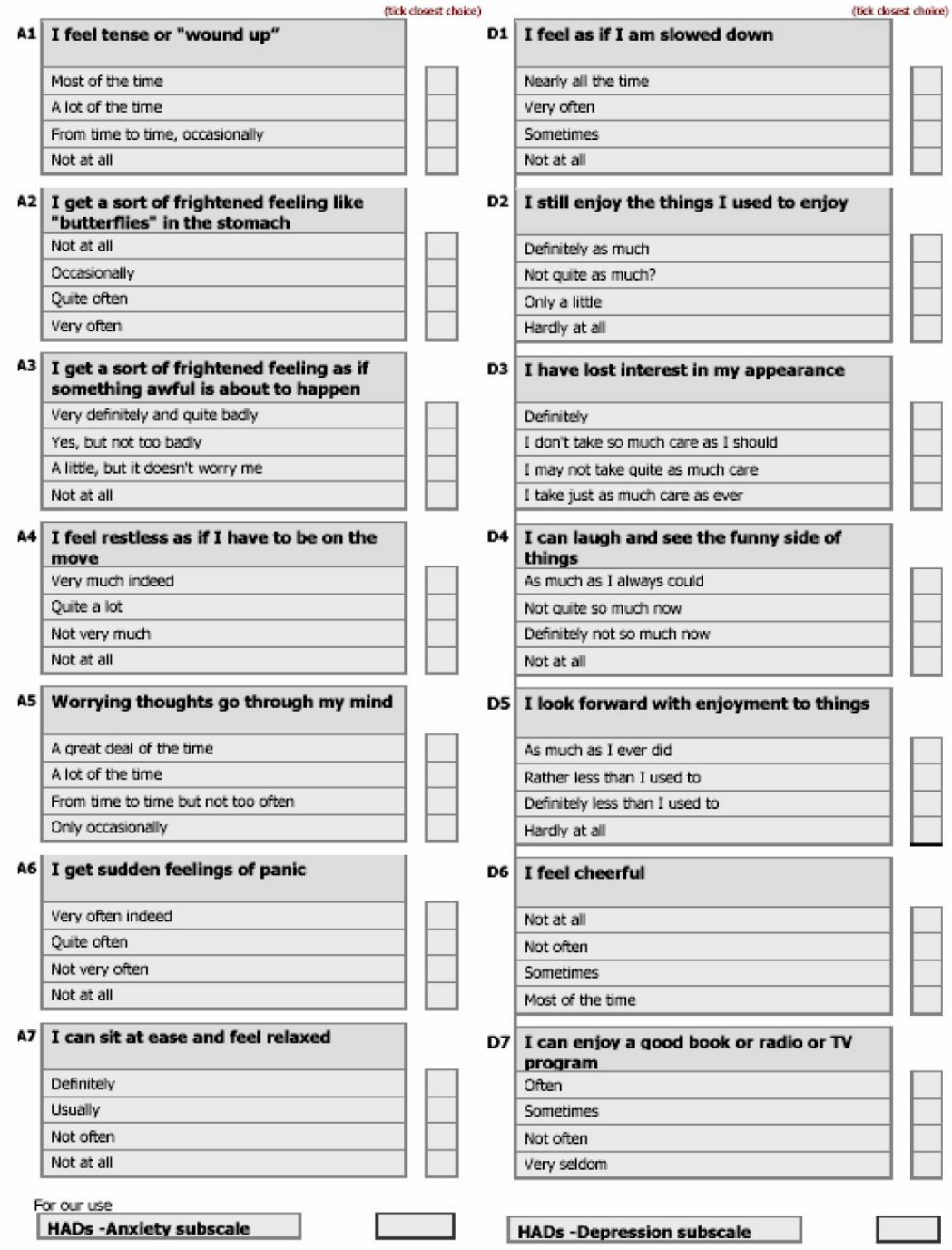
DLQI Score:

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** ☐

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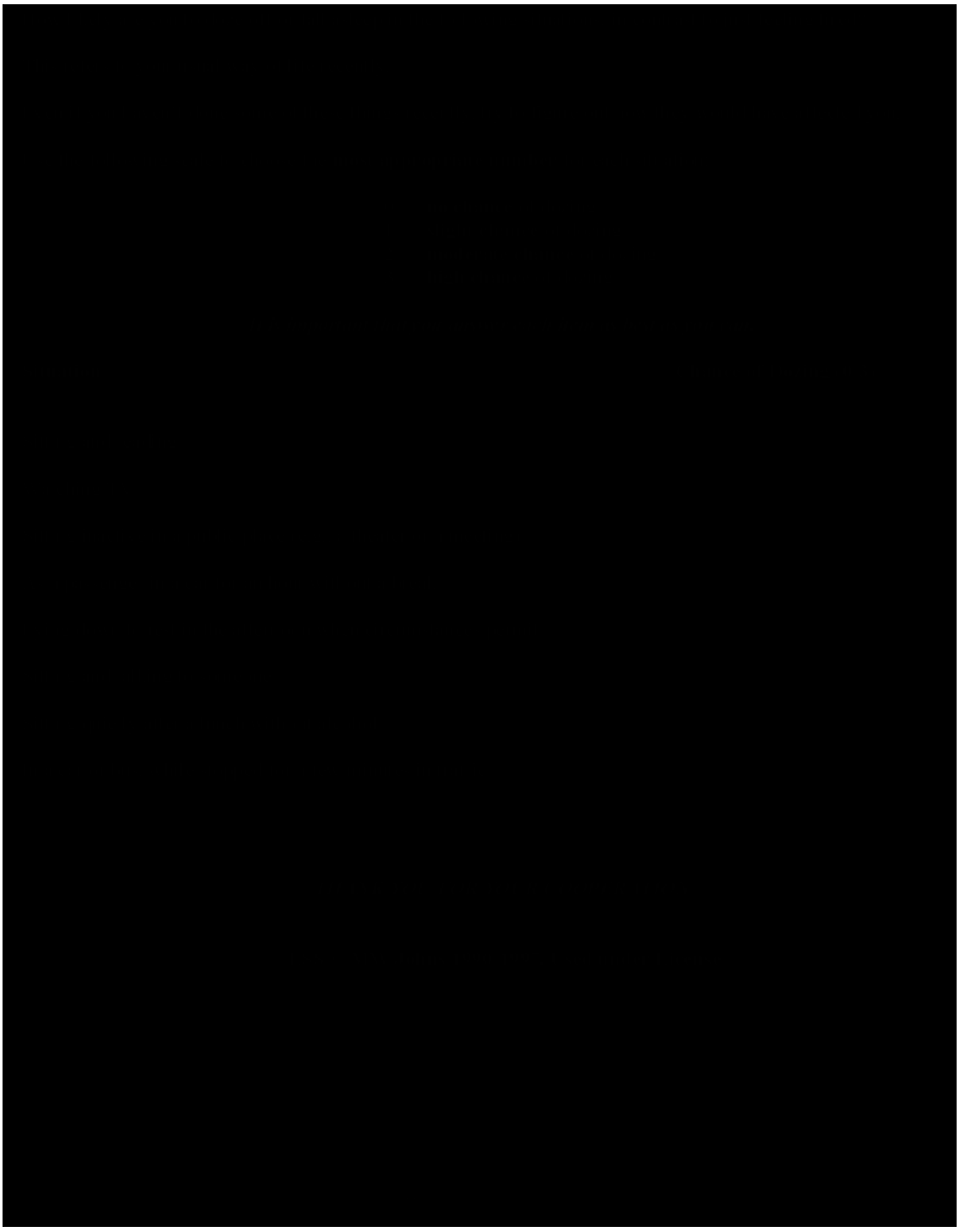
APPENDIX G EPWORTH SLEEPINESS SCALE



CLINICAL STUDY PROTOCOL MTI-106

SUMMARY OF CHANGES

Drug Product Name:	Serlopitant
Study Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
IND No.:	117780
EudraCT No.:	2017-004210-25
ClinicalTrials.gov ID:	NCT03677401
Protocol Version:	3.0
Protocol Date:	21 March 2019
Replaces Version/Date:	2.1 / 02 July 2018

The following changes were made to the MTI-106 Clinical Study Protocol from Version 2.1 to Version 3.0.

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.
8.8.2 Key Secondary Efficacy; 8.9.2 Repeated Measures Analysis	Removed two key secondary efficacy endpoints	These secondary efficacy endpoints were unnecessary for evaluation of the study drug.
4.1 Study Population	Increased study population to 280 subjects	In completed Phase 2 pruritus studies, with variations in screening methodologies, placebo responder rates have varied between [redacted]% and [redacted]% and serlopitant rates between [redacted]% and [redacted]%. The sample size was recalculated as a result of this observation.
8. Statistical methods; 8.11 Interim Analyses	Added optional interim analysis	An interim analysis may be performed to assess the adequacy of the sample size assumptions.
8.1 Decision Rule and Sample Size	Removed two key secondary efficacy endpoints, increased sample size	Please see comments for section 4.1 and 8/8.1.
8.2 Statistical methods	Updated Syntax to replace individual day calculations with week 1 calculation	Correction as key secondary endpoints were removed.

ADMINISTRATIVE CHANGES:

Section(s)	Summary of Change
Title page	Updated protocol version number and release date, added Clinical Trials.gov ID number
Signature Page for Investigator(s)	Updated protocol version number and release date, added Clinical Trials.gov ID number
Sponsor Protocol Approval Signature(s)	Updated protocol version number and release date, added Clinical Trials.gov ID number
Table of Contents	Updated

Throughout	Updated protocol version in footer; Edited formatting and corrected minor typos and inconsistencies

CLINICAL STUDY PROTOCOL

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
IND No.:	117780
Eudra CT:	2017-004210-25
ClinicalTrials.gov ID:	NCT03677401
Protocol No.:	MTI-106
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 PRINCIPAL INVESTIGATOR(S)

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
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Protocol Version/Date:	Verson 3.0/21 March 2019
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 Practices, and the Declaration of Helsinki.

Principal Investigator's printed name

Principal Investigator's signature

Date (DD-MMM-YYYY)

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
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Protocol No.:	MTI-106
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

PROTOCOL SYNOPSIS

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Pruritus in Adults With Prurigo Nodularis
Protocol Number:	MTI-106
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Efficacy objective: To assess the efficacy of serlopitant for the treatment of pruritus in adults with prurigo nodularis. Safety objective: To assess the safety and tolerability of repeated oral doses of serlopitant in adults with prurigo nodularis.
Study Design:	This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with prurigo nodularis (PN). Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 3- or 5-week follow-up period. The study will consist of three periods, for a total study period of 15 to 19 weeks: • Screening period: 2-4 weeks • Treatment period: 10 weeks • Follow-up period: 3 or 5 weeks During the screening period, all subjects will undergo eligibility evaluation and will be assessed for chronic pruritic conditions frequently associated with PN. Subjects who present with idiopathic PN at screening may require additional assessments as deemed necessary by the investigator (e.g. endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis, skin biopsy for subjects with signs or symptoms of bullous pemphigoid or cutaneous T-cell lymphoma, urea breath test for *Helicobacter pylori*, or allergy testing). All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of electronic diary (eDiary) screening data. Subjects who require a screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit. Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study. At the Baseline visit (Day 1), eligible subjects will be randomly assigned to receive study drug (serlopitant 5 mg or placebo). Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Day 1). Starting on Day 2, subjects will take one tablet per day. Study drug may be taken with or without food.

	The primary efficacy endpoint will be assessed at Week 10 of treatment. Subjects who complete the 10-week treatment period and required follow-up period may be given the opportunity to enroll in a one-year open-label safety study with daily oral doses of serlopitant 5 mg.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor blinded safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 280 subjects will be randomized.
Study Population:	The study will consist of adult subjects with pruritus associated with PN. Inclusion Criteria (Subjects must meet the following criteria to be randomized into the study): 1. Male or female, age 18 years or older at consent. 2. A diagnosis of PN, defined by the presence of at least ten pruriginous nodules secondary to chronic pruritus present on at least two different body surface areas (e.g. both arms, one arm and one leg, one arm and the anterior trunk, or anterior and posterior trunk). 3. The worst pruritus is identified to be within the areas of the PN lesions. 4. Subject has idiopathic PN OR the subject has an identified pruritic condition associated with the PN and has persistent pruritus despite at least 6 weeks of optimized and stable treatment of the underlying condition prior to the Baseline visit, and is willing to continue the treatment during the study. 5. Worst-Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the 24-hour period prior to the Screening visit. 6. Average weekly WI-NRS score ≥ 6.5 in each of the 2 weeks (14 days) immediately prior to Baseline visit, as recorded in the eDiary. 7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last dose of study drug. 8. Willing and able (as demonstrated by a ≥ 70% eDiary completion rate in the two weeks prior to Baseline visit) to complete daily eDiary entries within a consistent timeframe for the duration of the study. 9. 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. Prior treatment with serlopitant. 2. Active pruritic skin disease, other than PN, within 6 months prior to randomization (with the exception of acute dermatoses such as contact dermatitis, sunburn, viral exanthem, which have been resolved for longer than 4 weeks). 3. Treatment with any of the following therapies within 4 weeks prior to randomization.

	a. Other neurokinin-1 receptor antagonists (e.g., aprepitant, fosaprepitant, rolapitant). b. Systemic or topical immunosuppressive/immunomodulatory therapies (including but not limited to corticosteroids, phosphodiesterase-4 inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, interferon-gamma, thalidomide, or phototherapy). c. Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists (e.g. naloxone, naltrexone)). d. Strong cytochrome-P 3A4 inhibitors. e. Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn. 4. Treatment with topical anti-pruritic therapies (e.g., menthol, camphor, pramoxine, capsaicin) within 2 weeks prior to randomization. 5. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer. 6. Treatment with any investigational therapy within 4 weeks (8 weeks for investigational biologic therapies) or 5 half-lives prior to randomization, whichever is longer. 7. Serum creatinine, total bilirubin, alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal during screening. 8. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy. 9. History of malignancy within 5 years prior to randomization, with the exception of actinic keratosis, completely treated and non-metastatic cutaneous basal cell carcinoma or squamous cell carcinoma of the skin. 10. 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 randomization. 11. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt. 12. Documented history of parasitic infection, including skin parasites such as scabies, within 8 weeks prior to randomization. 13. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject. 14. History of hypersensitivity to serlopitant or any of its components. 15. Currently pregnant or breastfeeding female subject. 16. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated

	assessments (e.g. extended international travel) during the subject's participation in the study.
Study Drug:	Serlopitant 5 mg oral tablets and matching placebo.
Dosage:	Serlopitant: 5 mg once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period. Matching placebo: Once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period.
Primary Efficacy Endpoint:	The primary efficacy endpoint is the WI-NRS 4-point responder rate at Week 10.
Secondary Efficacy Endpoints:	The key secondary efficacy endpoints are as follows: • WI-NRS 4-point responder rate at Week 4 • Change from baseline in Dermatology Life Quality Index (DLQI) to Week 10 Additional secondary efficacy endpoints are as follows: • Change from baseline in WI-NRS to other timepoints • WI-NRS 4-point responder rate at Week 2 • WI-NRS 3-point responder rate at Weeks 2, 4 and 10 • Change from baseline in Investigator's Global Assessment of PN Activity to Weeks 2, 4 and 10 • Change from baseline in Investigator's Global Assessment of PN Stage to Weeks 2, 4 and 10
Safety Endpoints:	Safety endpoints are as follows: • Incidence of treatment-emergent adverse events and serious adverse events (SAEs) • Changes from baseline in clinical laboratory parameters following study drug exposure • Changes from baseline in vital sign and electrocardiogram (ECG) parameters following study drug exposure • Changes from baseline in the Hospital Anxiety and Depression Scale (HADS) • Changes from baseline in the Epworth Sleepiness Scale (ESS)
Decision Rule and Sample Size:	This study will use a 5% two-sided alpha level. Hierarchical testing in which statistical significance for the key secondary efficacy endpoints requires statistical significance for the primary endpoint. The target sample size of 280 randomized and dosed subjects (140 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. Completed Phase 2 studies indicate that placebo responder rates vary between CCI% and CCI% and serlopitant rates between CCI% and CCI%. A sample size of 280 subjects provides >90% power assuming a placebo responder rate of CCI% and a serlopitant rate of CCI%.
Statistical Methods:	Efficacy analyses will be based upon an intent-to-treat philosophy. The primary efficacy population will be the Intent-to-Treat (ITT) population that will include

	all randomized subjects who were dispensed study drug. Analyses performed on the Per Protocol population will be considered supportive. Subjects will be analyzed within the treatment group to which they are randomized. Efficacy Analyses: The primary efficacy endpoint is a binary variable taking on values of responder or non-responder. Subjects will be considered a responder if they have at least a 4-point reduction in WI-NRS between baseline and Week 10. Missing data imputation will be used for subjects who fail to complete the eDiary at Week 10, unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. The primary endpoint will be summarized with descriptive statistics by treatment group and study week. The difference in the primary efficacy outcome measure between treatment groups will be tested using a Cochran Mantel Haenszel test controlling for the stratification factors. Testing of the key secondary efficacy endpoints will also be employed.
	Safety Analyses: The incidence of all adverse events (AEs) and treatment-related AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. An overview of AEs, which includes subject incidence of AEs, treatment-related AEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Clinical safety laboratory values will be measured by a central laboratory. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Graphs of laboratory values over time will also be produced. Subjects with clinical laboratory values outside of the normal reference range at any post-baseline assessment will be summarized. Shifts from baseline laboratory values will be tabulated. The overall ECG assessment (abnormal or normal) will be summarized along with a summary of how many subjects developed a post treatment abnormal result. Summary statistics for the HADS and ESS actual values and change from baseline will be presented by scheduled visit.
Study Sites:	Approximately 50 study sites.
Expected Duration of Subject's Participation	15-19 weeks: 2-4 weeks of screening, 10 weeks of treatment, and a follow-up period of 3 or 5 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone, corticotropin
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CMH	Cochran Mantel Haenszel test
CNS	Central Nervous System
CRO	Contract Research Organization
CYP3A4	Cytochrome-P 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ESS	Epworth Sleepiness Scale
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAART	Highly active antiretroviral therapy
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-A	Investigator's Global Assessment of Prurigo Nodularis Activity
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
LFC	Liquid filled capsule
LH	Luteinizing hormone
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor

NOAEL	No observed adverse effect level
NRS	Numeric Rating Scale
PET	Positron Emission Tomography
PI	Principal Investigator
PD	Pharmacodynamics
PDE-4	Phosphodiesterase-4
PK	Pharmacokinetics
PN	Prurigo nodularis
PP	Per Protocol
QOL	Quality of life
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus in Prurigo Nodularis

Prurigo nodularis (PN) is a distinctive and easily diagnosable chronic skin condition characterized by the presence of multiple highly pruritic and often symmetrically distributed nodules and papules on the skin (Jorizzo 1981). The nodules and papules in PN can range in size from approximately 0.5 to 3.0 cm and often appear hyperkeratotic, sometimes crateriform, in appearance. Plaques are occasionally present, and the lesions of PN frequently exhibit other features secondary to prolonged and severe scratching behavior, such as post-inflammatory hyperpigmentation, erosion, ulceration, crusting, and bleeding (Zeidler 2016).

PN, a long-term reaction to the chronic scratching and picking of patients with chronic pruritus (Zeidler 2016), is a skin condition seen predominantly in older adults, with median prevalence age in the 50s and 60s and a slight female preponderance (Iking 2013, Tan 2014, Ständer 2013). In one patient population survey, pediatric patients accounted for <2% of the total population, with the youngest patient 11.9 years of age (Iking 2013). Although only limited epidemiology data for PN have been published, a claims-based analysis commissioned by Menlo Therapeutics suggest that the United States (US) prevalence may be in the range of ~ 355,000 affected individuals. Based on a quantitative survey of 73 dermatologists conducted in parallel with the claims-based analysis, approximately 23% of patients with PN have an underlying atopy-related condition, while over 50% are considered to be idiopathic (Navigant 2017). The median duration of disease burden has been reported to be 6-7 years (Iking 2013, Tan 2014, Schuhknecht 2011).

The dominant symptom in PN is an intense and chronic pruritus that is associated with a high degree of patient burden and restricted quality of life (QOL) (Zeidler 2016). As measured by global scales of pruritus intensity (numeric rating scale (NRS) and visual analog scale (VAS)), median levels of pruritus intensity have been reported to be 7-8 points (Iking 2013, Tan 2014, Schuhknecht 2011). The pruritus experienced in PN can often prevent patients from adequately performing their daily activities (Vaidya 2008), and patients with PN have been found to suffer from greater rates of depression and anxiety than control groups in numerous studies (Jorgensen 2016, Rowland Payne 1985, Dazzi 2011).

1.2 Conditions Associated With Prurigo Nodularis

As PN is considered to be a disease induced by chronic pruritus and ongoing scratching activity, a variety of chronic pruritic conditions have been identified as potential underlying etiologies for the pruritus, including atopic dermatitis (AD), other inflammatory or bullous skin diseases, chronic renal failure, human immunodeficiency virus (HIV) infection, hepatitis C infection, and multifactorial disease (i.e. two or more co-existent conditions associated with chronic pruritus) (Fostini 2013, Lee 2005). The mechanisms linking chronic pruritus to the development of PN are not clear, as only a subset of patients with chronic pruritus develop PN, and over half of patients with PN have no underlying etiology identified. Even when specific underlying conditions are identified, management of these condition(s) does not usually result in resolution of PN signs or symptoms, nor can all underlying conditions be treated. For example, PN has been observed in patients with HIV adequately managed with

highly active antiretroviral therapy (HAART) (Zancanaro 2006), in patients with intractable cholestatic pruritus (Bergasa 2011), in patients with inactive hepatitis (Halvorsen 2015), and commonly in patients with renal failure despite hemodialysis therapy (Goeksel 2013). These data point to a high level of unmet medical need in the overall PN population, as the majority of patients with PN either have no underlying condition identified that can be treated, or treatment of the underlying condition is inadequate to control their PN (Wallengren 2004).

1.3 Current Treatment Options for Prurigo Nodularis

Treatment of PN remains a challenging and extremely frustrating experience for both patients and physicians. In the majority of cases, responses are limited and unsatisfactory, and once the cycle of pruritus-excoriation-pruritus begins, it is difficult to stop. Identification and treatment of underlying chronic pruritic conditions is often the first step in management of PN. If this does not result in resolution of the pruritus, or if no underlying condition is identified, treatment specifically for PN and its associated pruritus is implemented.

First-line pruritus therapies, including topical agents such as topical corticosteroids and calcineurin inhibitors, often provide inadequate response (Saco 2015) and the therapeutic ladder for PN involves systemic agents with progressively riskier safety profiles. These include naltrexone, gabapentin, mirtazapine, phototherapy, intravenous immunoglobulin (IVIG), powerful immunosuppressants such as methotrexate and cyclosporine, and thalidomide (Ständer 2015b, Spring 2014, Feldmeyer 2012, Lim 2016). None of these therapies are indicated for the treatment of PN, and their usage is often based on limited evidence, such as case reports or small open-label studies.

1.4 Substance P and the Neurokinin-1 Receptor

Repeated itching, scratching, and picking over long time periods serve as the pathophysiological basis for the development of PN. Although different underlying disease states may be responsible for the chronic pruritus, the distinctive and easily recognizable features of PN point to a common final pathway resulting in this unique clinical presentation.

Immunohistochemical staining studies of PN biopsies have demonstrated that nerve fibers immunoreactive for Substance P (SP) are found in increased numbers in lesional skin compared to non-lesional skin or controls (Abadía Molina 1992), suggesting a role for SP signaling in PN. These findings are consistent with the robust body of evidence indicating the key role of SP signaling through its primary receptor, the neurokinin-1 receptor (NK_1-R), in the transmission of itch across multiple disease states (Santini 2012, Akiyama 2015, Crowe 1994, El-Nour 2006, Lotts 2014, Hon 2007, Ward 2004, Slattery 2011).

SP is an undecapeptide that belongs to the tachykinin family of neuropeptides, a group that also includes neurokinin A and neurokinin B (Hökfelt 2001). SP has been implicated in a number of biological functions, both physiological and pathophysiological, including pruritus perception, vomiting reflex, pain perception, and immunomodulatory responses (Lotts 2014, Andoh 1998, Steinhoff 2014). The biological actions of SP are mediated by tachykinin receptors, which consist of seven hydrophobic transmembrane domains coupled to G-proteins. Three tachykinin receptors have been identified: the neurokinin-1, neurokinin-2,

and neurokinin-3 receptors (Harrison 2001). The NK_1-R 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, include central and peripheral neurons, keratinocytes, and mast cells.

NK_1-R stimulation has been shown to be an important pathway for pruritus perception (Ständer 2015a). 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).

1.5 Serlopitant

1.5.1 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.

1.5.2 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 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.

1.5.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

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

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

squares mean difference compared to placebo was 5.8 mm, 13.2 mm, and 14.2 mm for serlopitant 0.25 mg, 1 mg, and 5 mg, respectively.

The frequency of 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.

Potential Risks and Benefits: 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 treatment of pruritus in patients with PN. The potential benefits of continued clinical study outweigh the potential risks.

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

2 STUDY OBJECTIVES

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

The safety objective of this study is to assess the safety and tolerability of repeated oral doses of serlopitant in adults with PN.

3 STUDY DESIGN

3.1 Overall Study Design

This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with PN. The study will be conducted at approximately 50 study sites. Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 3 or 5-week follow-up period. The required follow-up period is defined as a minimum of 3 weeks for those subjects who will enroll in the one-year open-label safety study (MTI-107) on the date of the follow-up visit, and as 5 weeks for those subjects who will not be enrolled in the one-year open-label safety study of serlopitant. Should a subject present for the follow-up visit prior to 5 weeks after the last dose of study drug and be excluded from participation in the one-year study for any reason, the subject will be required to return at 5 weeks after the last dose of study drug for a complete follow-up visit.

This study will consist of three periods, for a total study period of 15-19 weeks:

- Screening period: 2-4 weeks
- Treatment period: 10 weeks
- Follow-up period: 3 or 5 weeks

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

During the screening period, all subjects will undergo eligibility evaluation and will be assessed for chronic pruritic conditions frequently associated with PN. Subjects who present with idiopathic PN at screening may require additional assessments as deemed necessary by the investigator (e.g. endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis, skin biopsy for subjects with signs or symptoms of bullous pemphigoid or cutaneous T-cell lymphoma, urea breath test for *Helicobacter pylori*, or allergy testing).

All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of electronic diary (eDiary) screening data. Subjects who require screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred following discussion with the medical monitor should more than 31 days be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition).

Screening procedures may be repeated (i.e., the subject may be rescreened) following discussion with the medical monitor should the subject have had difficulty complying with eDiary assessments, require further training in the assessments, or have other relevant needs that may delay enrollment in the study but are not expected to impact safety or efficacy assessments.

Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study.

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

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

Subjects who complete the 10-week treatment period and required follow-up period may be given the opportunity to enroll in a one-year open-label safety study (MTI-107) with daily oral doses of serlopitant 5 mg.

3.2 Rationale for Study Design and Dose Selection

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

patients with chronic pruritus, serlopitant 5 mg and 1 mg taken daily for 6 weeks were superior to placebo for the reduction of pruritus, in both the overall study population and the subgroup of subjects with an atopic diathesis.

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

The current MTI-106 study is designed to confirm the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in patients with PN. 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. Over 250 subjects have been exposed to serlopitant at doses of 5 mg tablet-equivalent daily for at least 6 weeks, and ~ 40 subjects have been exposed up to one year. Human CNS PET RO data for serlopitant in healthy young males (Study P002) demonstrated that a serlopitant 5 mg LFC once daily dose is likely to achieve ~ 94% NK_1 RO at steady state.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

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

3.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- WI-NRS 4-point responder rate at Week 4
- Change from baseline in Dermatology Life Quality Index (DLQI) to Week 10

3.3.3 Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints are as follows:

- Change from baseline in WI-NRS to other timepoints
- WI-NRS 4-point responder rate at Week 2
- WI-NRS 3-point responder rate at Weeks 2, 4 and 10
- Change from baseline in Investigator's Global Assessment of PN Activity (IGA PN-A) to Weeks 2, 4 and 10
- Change from baseline in Investigator's Global Assessment of PN Stage (IGA PN-S) to Weeks 2, 4 and 10

3.3.4 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs and SAEs
- Change from baseline in clinical laboratory parameters following study drug exposure
- Change from baseline in vital sign and 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)

3.4 Safety Review

3.4.1 Safety Monitoring Team

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

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 280 adult subjects with pruritus associated with PN will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. A diagnosis of PN, defined by the presence of at least ten pruriginous nodules secondary to chronic pruritus present on at least two different body surface areas (e.g. both arms, one arm and one leg, one arm and the anterior trunk, or anterior and posterior trunk).
3. The worst pruritus is identified to be within the areas of the PN lesions.
4. Subject has idiopathic PN OR the subject has an identified pruritic condition associated with the PN and has persistent pruritus despite at least 6 weeks of optimized and stable treatment of the underlying condition prior to the Baseline visit, and is willing to continue the treatment during the study. Please refer to Section 5.7.1.
5. WI-NRS score ≥ 7 in the 24-hour period prior to the Screening visit.
6. Average weekly WI-NRS score ≥ 6.5 in each of the 2 weeks (14 days) immediately prior to Baseline visit, as recorded in the eDiary.
7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per

year) from the time of the Screening visit until 5 weeks after last dose of study drug. Please refer to Section 7.1.5 for acceptable methods of contraception.

8. Willing and able (as demonstrated by a ≥ 70% eDiary completion rate in the two weeks prior to Baseline visit) to complete daily eDiary entries within a consistent timeframe for the duration of the study.
9. 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. Prior treatment with serlopitant.
2. Active pruritic skin disease, other than PN, within 6 months prior to randomization (with the exception of acute dermatoses such as contact dermatitis, sunburn, viral exanthem, which have been resolved for longer than 4 weeks). Please refer to Section 5.7.1.
3. Treatment with any of the following therapies within 4 weeks prior to randomization.
    a. Other NK_1-R antagonists (e.g., aprepitant, fosaprepitant, rolapitant).
    b. Systemic or topical immunosuppressive/immunomodulatory therapies (including but not limited to corticosteroids, phosphodiesterase-4 (PDE-4) inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, interferon-gamma, thalidomide, or phototherapy).
    c. Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists (e.g. naloxone, naltrexone)).
    d. Strong CYP3A4 inhibitors (see Appendix B).
    e. Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn.
4. Treatment with topical anti-pruritic therapies (e.g., menthol, camphor, pramoxine, capsaicin) within 2 weeks prior to randomization (see Section 5.7.2).
5. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer.
6. Treatment with any investigational therapy within 4 weeks (8 weeks for investigational biologic therapies) or 5 half-lives prior to randomization, whichever is longer.
7. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) during screening.
8. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease or history of thyroid malignancy.

9. History of malignancy within 5 years prior to randomization, with the exception of actinic keratosis, completely treated and non-metastatic cutaneous basal cell carcinoma or squamous cell carcinoma of the skin.
10. 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 randomization.
11. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt.
12. Documented history of parasitic infection, including skin parasites such as scabies, within 8 weeks prior to randomization.
13. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject.
14. History of hypersensitivity to serlopitant or any of its components.
15. Currently pregnant or breastfeeding female subject.
16. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g. extended international travel) during the subject's participation in the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

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

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

The tablets will be supplied in bottles, with 18 tablets per bottle. One bottle will be issued via Interactive Web Response System (IWRS) at baseline and at Weeks 2 and 4, and two bottles will be issued via IWRS at Week 6. A total of 5 bottles will be dispensed to subjects completing 10 weeks of study drug treatment.

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

5.2 Labeling and Study Drug Accountability

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

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

5.3 Dosing Regimen

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

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

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

5.6 Study Drug Discontinuation

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

- A female subject desires to become pregnant at the current time, stops contraception or expels her intrauterine device/implant, or becomes pregnant
- A female subject has new breast findings (e.g. a palpable mass or abnormal mammography, discharge), or has abnormal vaginal discharge or bleeding
- The subject decides to discontinue study drug treatment, or withdraws consent from the study
- The subject receives a strong CYP3A4 inhibitor (See Appendix B)
- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion; this may include the development of persistently (2 successive occasions) abnormal thyroid function tests (TSH >10, or TSH > 6 with low free T4; TSH <0.1, or TSH < 0.35 with high free T4); abnormal morning prolactin, cortisol, or corticotropin levels; or signs and symptoms of adrenal insufficiency

- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion, including evidence that the subject does not meet inclusion/exclusion criteria intended primarily for safety reasons, or a persistent lack of adherence to study procedures

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

Subjects who discontinue treatment with study drug prior to completing the treatment period will enter a 5-week follow-up period following the last dose of study drug in addition to a Follow-up visit (see Section 3.1, Section 6.5.10). Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued from study drug.

5.7 Prior, Concomitant, and Excluded Therapies

Prior therapies (including over-the-counter medications) used to treat the signs and symptoms of PN within the prior 2 years will be recorded for each subject at the Baseline visit.

Concomitant therapies include any therapies (including over-the-counter medications and bland emollients) used by a subject from initiation of study drug treatment through the follow-up period. A record of all medications used will be maintained for each subject throughout the study. Reported information will include a description of the type of drug, treatment period, dosing regimen, the route of administration, and drug indication. The use of any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements, emollient use, and routine preventative immunizations.

5.7.1 Allowed Therapies and Treatment Goals for Underlying Conditions

Treatment of an underlying, treatable chronic pruritic condition is allowed, if stable for at least 6 weeks prior to the Baseline visit, and continued throughout the treatment period.

Treatment of the underlying systemic pruritic condition should be optimized per standard of care and treatment goals must be tailored based on age, sex, and concurrent health status and drug tolerance. While resolution of metabolic or endocrine disorders or eradication of an underlying infection may not always be feasible, every effort should be made to ensure the condition is well controlled, to prevent or reduce exacerbations and to prevent limitation on the activities of daily living. When applicable, laboratory evidence of control should be obtained. For example, if renal insufficiency is implicated as causal for pruritus, treatment would be expected to have meaningfully reduced the creatinine (compared to that at the time of diagnosis) and to maintain the creatinine at < 2.5 the ULN; control of diabetes is supported by a hemoglobin-A1c of < 7.5%; control of thyroid disease is supported by normalization of the thyroid stimulating hormone (TSH) or by a TSH within 1.5 times the ULN in elderly patients; iron deficiency is corrected with a serum iron within 0.8 times the lower limit of normal; eradication of *Helicobacter pylori* infection generally requires a negative urea breath

test and fecal antigen test and endoscopy; and the viral load should be undetectable if viral infections such as hepatitis B or hepatitis C, or HIV were previously diagnosed. Any previously active skin disease is considered to be well controlled if it is globally considered clear or almost clear (permissible to have post-inflammatory pigmentation, fine scale, faint pink erythema, barely perceptible induration/papulation, and no oozing or crusting).

Use of gentle cleansers and bland emollients (including those with urea) is encouraged for all subjects. If bland emollient use is elected, it must be initiated at least 2 weeks (14 days) prior to Baseline visit, and continued throughout the treatment period.

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

Leukotriene inhibitors will be permitted for treatment of conditions other than PN (e.g. asthma).

5.7.2 Excluded Therapies

Initiation or use of topical therapy with corticosteroids, calcineurin inhibitors, calcipotriene, PDE-4 inhibitors is not permitted within 4 weeks prior to the Baseline visit or throughout the treatment period, but such therapy may be initiated during the follow-up period if needed.

Initiation of bland emollient is not permitted within 2 weeks (14 days) prior to Baseline visit or throughout the treatment period, but such therapy may be initiated during the follow-up period if needed.

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

- NK_1-R antagonists (other than study drug)
- Systemic immunosuppressive/ immunomodulatory therapies (including but not limited to systemic corticosteroids, PDE-4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, thalidomide, interferon-gamma, or phototherapy)
- Biologic therapies (other than therapies such as insulins, vaccines)
- Strong CYP3A4 inhibitors (See Appendix B)
- Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn
- Any investigational therapy

The following therapies and activities are excluded from the Screening visit through the treatment period, and use is discouraged, though permitted, through the follow-up period:

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

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

5.7.3 Rescue Therapies

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

5.8 Assignment to Treatment

5.8.1 Randomization

Eligible subjects will be randomized to receive serlopitant 5 mg or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by the subject's reported WI-NRS score for the 1-week period prior to the Baseline visit (6.5 to < 9, 9 to 10).

An IWRS will be used to perform the randomization.

5.8.2 Blinding

This study will be conducted as a double-blind study with the treatment assignment concealed from the subjects, the investigators and their staff, the Sponsor, and any designees of the Sponsor as required. The placebo will be formulated to be indistinguishable from the active study product. Study materials will be packaged and issued in a manner designed to maintain the blind for subjects and all study personnel involved in the direction and execution of study procedures, study assessments, and collection of data. The randomization code for each subject will be available to the sites for use only in an emergency situation. For details of the procedure for unblinding of individual subjects in cases of emergency see Section 7.6.

5.9 Treatment Compliance

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

6 STUDY SCHEDULE AND ASSESSMENTS

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

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

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

6.1.2 Investigator's Global Assessment of PN Activity

The IGA PN-A is an instrument used to assess the overall activity 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-A uses clinical characteristics of excoriations, crusting, and/or bleeding as guidelines for the overall activity assessment. The number of pruriginous lesions should not be considered for this assessment. IGA PN-A scores will be captured as outlined in 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 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 of number of nodules and their thickness as guidelines for the overall severity assessment. IGA-PN-S scores will be captured as outlined in Appendix A. Each assessment during the study must be done by the 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.

6.1.4 Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI) is a dermatology specific QOL instrument designed to assess the impact of the skin disease on a subject's QOL over the prior week. It is a ten-item questionnaire that assesses overall 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 outlined in Appendix A.

6.1.5 PN Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as outlined in 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. The PI and designees will be trained on the use of the camera and the appropriate lighting and positioning of the representative area with PN involvement. Detailed instructions will be provided in the 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 as outlined in Appendix A.

6.2.1 Vital Signs

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

6.2.2 Physical Examination

Physical examinations, including height and weight measurements, will be performed as outlined in Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the screening visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. 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 outlined in Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified.

Detailed instructions regarding sample collection, preparation, and shipment can be found in the laboratory manual. Laboratory assessments will include the following, and are ideally performed in the morning, particularly at visits with endocrine assessments (Screening, Week 10, Follow-up):

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, uric acid, total protein, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel
- Iron studies: ferritin, serum iron
- Serology: hepatitis B and C serology, HIV
- Serum IgE
- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Endocrine: TSH, free T4, cortisol, corticotropin (adrenocorticotropic hormone, ACTH), prolactin
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)
- Optional study provided in lab test kits for use at Screening only: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis

- Additional optional studies will be supported through local procedural and/or laboratory assessments, including, but not limited to, 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.
- Standard cosyntropin stimulation testing should be performed on subjects with low cortisol level (i.e. < 3.0 mcg/dL); the investigator should discuss low cortisol (and relevant low corticotropin) results with the medical monitor.

6.2.4 Electrocardiogram

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

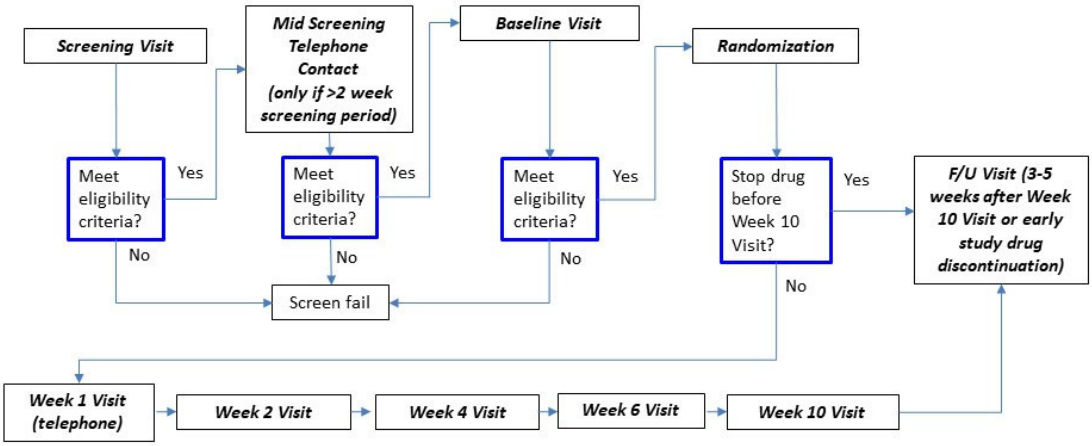
6.3 Pharmacokinetic Measurements

Sparse PK sampling will involve collecting one PK sample at each of the Week 2, Week 4, and Week 10 visits as outlined in Appendix A. The date and time of dosing prior to PK sample collection and date and time of PK sample collection will be collected. The plasma concentrations of serlopitant and metabolites will be determined and data used for population PK analysis. Detailed instructions regarding PK sample collection, preparation, and shipment can be found in the laboratory manual.

6.4 Subject Flow Diagram

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

Figure 1 Subject Flow Diagram



6.5 Study Visits

The following sections describe the procedures and assessments to be performed at each study visit. Details of each procedure and assessment can be found in Sections 6.1, 6.2, and 6.3. The timing of each study visit is relative to the day of randomization (Baseline).

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

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

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

6.5.1 Screening Period

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

All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of eDiary screening data. Subjects who require screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred following discussion with the medical monitor should more than 31 days be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition).

Screening procedures may be repeated (i.e., the subject may be rescreened) following discussion with the medical monitor should the subject have had difficulty complying with eDiary assessments, require further training in the WI-NRS assessments, or have other relevant needs that may delay enrollment in the study but are not expected to impact safety or efficacy assessments.

6.5.2 Screening Visit

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

- Obtain written informed consent prior to any protocol-mandated procedures, including the stopping of any excluded therapies
- Collect demographic information (sex, date of birth, race, ethnicity)
- Ask subject to complete the WI-NRS scale on paper
- Register Screening visit into the IWRS
- Obtain ECG
- Obtain vital signs
- Review subject's medical history (including prior medications)
  - Record only significant/relevant medical history, to include the onset date of PN (as specifically as known) and presence of an underlying condition (if any)
  - Designate the primary and any concurrent medical conditions that are identified as pruritic conditions underlying the PN
  - 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) and confirm clinical diagnosis of PN
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
  - Serology
  - Serum IgE
  - Iron studies
  - Optional: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis
  - Optional: additional assessments (refer to Section 6.2.3)
- Review subject's tentative eligibility according to the Inclusion/Exclusion criteria
  - The results of all screening evaluations, including laboratory and ECG results, must be reviewed for clinical significance by the PI or designee, and may require further evaluation, prior to randomization of the subject on Baseline visit
- Schedule the Baseline visit and all future study visits to ensure subject's availability and visit compliance with the protocol visit windows
- Provide a menstrual diary to female subjects who report periodic menstruation
- Provide eDiary with instructions
- Confirm next scheduled visit

6.5.3 Mid-Screening Telephone Contact (for subjects longer than 14 days in Screening)

During this telephone contact the following procedures are to be performed:

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

6.5.4 Baseline Visit

The Baseline visit occurs between 14 to 31 days after the screening visit, depending on the required washout period following discontinuation of excluded therapies. Eligibility must be confirmed prior to randomization. At the Baseline visit, the following procedures and assessments are to be performed, preferably in the order shown below:

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Assess and record any changes in the subject's medical history
  - Female subjects should be queried regarding history of, or current, breast masses or abnormal discharge, and history of mammography (if applicable), and history of abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess AE's and record SAEs caused by protocol-mandated interventions
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential and confirm the subject has a negative urine pregnancy test result prior to randomization (with positive or equivocal results confirmed by a serum pregnancy test)
- Confirm subject's eligibility based on the inclusion/exclusion criteria (to include review of eDiary compliance for eligibility)
- Randomize subject in IWRS if eligibility confirmed
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Dispense study drug; subjects will take loading dose of 3 tablets while on site
- Review eDiary for compliance, re-train subject as needed
- Assess and record any post-dose AEs and SAEs
- Confirm next scheduled visit

6.5.5 Week 1 Telephone Contact Visit

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

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

6.5.6 Week 2 Visit

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

- 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
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Collect returned study drug

- Utilize IWRS to assign new bottle of study drug
- Confirm next scheduled visit date

6.5.7 Week 4 Visit

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

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign new bottle of study drug
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.8 Week 6 Visit

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

- 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
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Perform targeted physical examination, including weight
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign new bottle of study drug
- Review eDiary for compliance, re-train subject as needed
- Confirm next scheduled visit

6.5.9 Week 10 Visit

The Week 10 visit occurs 70 days (± 7 days) after the Baseline visit. At the Week 10 visit, the following procedures and assessments are to be performed:

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Collect returned study drug
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Review eDiary for compliance, inform subject to continue entering WI-NRS score until Follow-up visit
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.10 Follow-up Visit

The required Follow-up visit occurs 21 or 35 (+7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early. The required follow-up period is defined as a minimum of 3 weeks for those subjects who will enroll in the one-year open-label safety study on the date of the follow-up visit, and as 5 weeks for those subjects who will not be enrolled in the one-year open-label safety study of serlopitant. Should a subject present for the follow-up visit prior to 5 weeks after the last dose of study drug and be excluded from participation in the one-year study for any reason, the subject will be required to return at 5 weeks after the last dose of study drug for a complete follow-up visit.

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

- Register visit into the IWRS
- Ask the subject to complete the HADS and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain vital signs

- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Obtain ECG
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
- Assess and record any AEs and SAEs
- Collect eDiary device, review eDiary for compliance

6.5.11 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) –GCP guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If provided, the reason (adverse event, study burden, lack of efficacy, other) a subject withdrew consent will be recorded in the electronic Case Report Form (eCRF). The PI or site staff must make every effort to contact subjects who are suspected of being lost to follow-up. Attempts to contact such subjects must be documented in the subject's source documents.

7 ASSESSMENT OF SAFETY

7.1 Definitions

7.1.1 Adverse Event

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

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

7.1.2 Serious Adverse Event

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

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

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

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

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

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

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

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

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

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

7.1.4 Deaths

Any deaths that occur from the time of informed consent to the follow-up visit, regardless of attribution, must be reported within 24 hours of investigator's awareness of the death. See Safety Form Completion Instructions for complete instructions.

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

7.1.5 Pregnancies and Contraception Requirements for Females

For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal, unless permanently surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female.

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

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

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

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

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

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

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

7.1.6 Worsening of Pruritus or PN

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

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

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

All AEs entered into the eCRF will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 study drug treatment or participation in the study is not the cause of the AE or SAE.

7.4 Reporting Serious Adverse Events to the Sponsor and Institutional Review Board or Ethics Committee

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

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

Please see the Safety Form Report Completion Instructions for safety reporting instructions.

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

7.5 Reporting Serious Adverse Events to Regulatory Authorities and Study Investigators

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

7.6 Emergency Unblinding

Emergency unblinding is available 24 hours per day/7 days per week and will be performed via IVRS. An investigator may unblind a subject's treatment assignment only when knowledge of the investigational product is essential for the welfare of a subject. There is no specific antidote for serlopitant and usual supportive medical management is recommended in the case of a medical emergency.

8 STATISTICAL METHODS

All statistical processing will be performed using SAS® unless otherwise stated. One interim analysis may be performed. Endpoints will be summarized with descriptive statistics by treatment group and visit. For continuous variables, the following information will be presented: n (number of subjects), mean, standard deviation, median, minimum and maximum. For categorical variables counts and percentages will be used. Summary statistics for imputed efficacy data will be reported based upon imputed data.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Subjects who withdrew from the study due to a lack of efficacy, or used an excluded therapy to treat worsening of pruritus or PN, will be defined as non-responder.

As one sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). As a second sensitivity analysis, a repeated measures model will be used on observed data. Additionally, a tipping point analysis will be done as a sensitivity analysis for the primary endpoint.

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

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

8.1 Decision Rule and Sample Size

This study will use a 5% two-sided alpha level. While the alpha level is two-sided, clinically relevant results require a serlopitant benefit. Statistical significance for the key secondary efficacy endpoints requires statistical significance for the primary efficacy endpoint (i.e. stepdown testing from primary to key secondary endpoints). The key secondary efficacy endpoints will be tested in order starting with the Week 4 WI-NRS 4-point responder rate, and then the change from baseline to Week 10 in DLQI.

The target sample size of 280 randomized and dosed subjects (140 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. Completed Phase 2 studies indicate that placebo responder rates vary between CCI% and CCI% and serlopitant rates between CCI% and CCI%. A sample size of 280 subjects provides >90% power assuming a placebo responder rate of CCI% and a serlopitant rate of CCI%.

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

8.2 Handling of Missing Data

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

The primary method of handling missing efficacy data will be MCMC multiple imputation. Subjects who withdrew from the study due to a lack of efficacy, or used an excluded therapy to treat worsening of pruritus or PN, will be defined as non-responder. Imputation will be conducted within each treatment group independently, so the pattern of missing observations in one treatment group cannot influence missing value estimations in another. For each imputation process, 25 imputations will be performed.

If a subject fails to complete their eDiary for the week prior to Week 10, the primary endpoint (WI-NRS) data will be missing, unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. If the Week 10 value is missing for any other reason, the change from baseline value will be based on imputed data. Missing Week 10 WI-NRS values from which the 4-point responder status is derived will be estimated by MCMC.

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

1. Using the daily eDiary data, calculate Baseline and Week 2 through Week 10 values by averaging available values. If any values are available, these will be used i.e. a minimum of 1 observation is required to compute a week's average.

2. From step 1, create a dataset for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing WI-NRS values in each dataset will be filled in using the MCMC method to generate 25 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset.

Syntax:

```
proc mi data=datain out=dataout seed=&seed. Nimpute=25 <options>;
  where trtpn=(TRT);   /* Note TRT = [1, 2]; depending on treatment group */;
  mcmc chain=single;
  var baseline week1 week2 week3 week4 week5 week6 week7 week8 week9
week10;
run;
```

3. From each complete dataset, the dichotomous responder rate will be determined. Each complete dataset will be analyzed as specified for the particular analysis.

Missing Week 10 DLQI data will be derived for the analysis using the method of MCMC multiple imputation. The following steps will be followed:

1. DLQI for Week 10 will be calculated as per scoring instructions.

2. From step 1, create a dataset for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing values in each dataset will be filled in using the MCMC method to generate 25 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset.

Syntax:

```
proc mi data=datain out=dataout seed=&seed. Nimpute=25 <options>;
  where trtpn=(TRT);   /* Note TRT = [1, 2]; depending on treatment group */;
  mcmc chain=single;
  var baseline week4 week10;
run;
```

3. Each complete dataset will be analyzed as specified for the particular analysis.

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

A total of 4 random seeds will be needed to impute missing data. Those random seeds have been pre-specified by using a random number generator:

8.3 Analysis Populations

The primary efficacy population will be the Intent-to-Treat (ITT) and will include all randomized subjects who were dispensed study drug. Subjects will be analyzed within the treatment group to which they are randomized.

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

The Per Protocol (PP) population will include all subjects in the safety population who complete the Week 10 evaluations without any significant protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). Analyses performed on the Per Protocol population will be considered supportive. The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Receives a strong CYP3A4 inhibitor (See Appendix B);
- Receives an excluded medication for treatment of pruritus or PN;
- Have not been compliant with the dosing regimen (i.e. subjects must comply with 80−120% of the expected dosage of study medication during participation in the study);
- Out of visit window at the Week 10 visit by ±7 days

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

8.4 Subject Disposition

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

8.5 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.6 Prior and Concomitant Medications

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

Prior therapies (including over-the-counter medications) used to treat the signs and symptoms of PN within the prior 2 years will be reported. Prior medications will be summarized by ATC level and preferred drug name and listed.

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

8.7 Treatment Compliance and Extent of Exposure

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

8.8 Efficacy Analyses

All efficacy endpoints will be summarized within the ITT and PP populations using descriptive statistics by time point and treatment. Results including averaged imputed values will be summarized at Baseline, Week 2 (if available), 4, 10 and Follow-up, and the change from baseline for these measures will be summarized at Week 2, 4, 10 and Follow-up. The WI-NRS and change from baseline will also be presented for each study day.

8.8.1 Primary Efficacy

The difference in the primary efficacy outcome measure (WI-NRS 4-point responder rate at Week 10) will be tested using a CMH test controlling for the 'as randomized' stratification factors. Conceptually the hypotheses being tested are:

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

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

8.8.2 Key Secondary Efficacy

The differences between treatment groups for the key secondary efficacy endpoint, Week 4 WI-NRS 4-point responder rate, will be the CMH test identical to the one used for the primary endpoint.

Change from baseline in DLQI to Week 10 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and stratification factor as fixed effects and the baseline DLQI as a covariate. Both least squares means and observed means will be presented.

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

The preceding tests are to be conducted for the ITT population and the PP populations.

8.8.3 Additional Secondary Efficacy

Additional secondary efficacy endpoints will include analyses analogous to the primary and key secondary efficacy analyses. Additional secondary efficacy endpoints which may be drawn from the primary and key secondary imputations (including all WI-NRS endpoints) will be analyzed using the imputed data. Additional secondary efficacy endpoints otherwise will be analyzed using available data. P-values will be included for descriptive purposes only.

8.9 Sensitivity Analyses

8.9.1 Last Observation Carried Forward

In the first set of sensitivity analysis, missing values will be imputed using LOCF. Data will be imputed using LOCF unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. Each primary and key secondary endpoint will be analyzed as it was using the multiply imputed data.

8.9.2 Repeated Measures Analysis

The second set of sensitivity analyses will be performed on observed data.

The dichotomized primary and key secondary WI-NRS endpoints will be analyzed with a repeated measures logistic regression model (generalized estimating equations), with the dichotomized endpoint as the dependent variable and treatment, stratification factor and visit (Weeks 2, 4, 10) as independent factors

Change from baseline in DLQI to Week 10 will be analyzed with a repeated measures ANCOVA, with treatment, stratification factor and applicable timepoints as independent factors and a covariate of baseline value.

8.9.3 Tipping Point Analysis

A sensitivity analysis for the handling of missing data for the primary efficacy endpoint will be carried out using a tipping point analysis.

8.10 Safety Analyses

8.10.1 Adverse Events

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

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

8.10.2 Clinical Safety Laboratory Results

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

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

8.10.3 Vital Signs

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

8.10.4 Electrocardiograms

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

8.10.5 Physical Exams

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

8.10.6 Menstrual Diaries

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

8.10.7 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.

8.10.8 Epworth Sleepiness Scale

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

8.11 Interim Analyses

An interim analysis may be performed once approximately 50% of subjects have available Week 10 efficacy assessments. The purpose of this is to assess the adequacy of the sample size assumptions. In order to maintain the integrity of the trial, no unblinding of investigators or Sponsor will occur. The interim analysis will be performed by an independent statistician.

No decrease in sample size will be considered; only an increase in sample size may be considered. Full details would be provided in a separate Interim Analysis Plan.

8.12 Population Pharmacokinetics Analysis

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

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 guideline. The protocol, ICF, other written subject information, and any proposed study advertising material must be submitted to the IRB or EC for written approval. IRB or EC approval of these documents will be provided to the investigator. The study will not start until the IRB or EC has granted its approval of the study materials and procedures.

Protocol amendments will be submitted to the IRB or EC as explained in Section 9.1. SAE information will be submitted to the IRB or EC as explained in Section 7.4.

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

9.7 Disclosure and Confidentiality

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

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

9.8 Records and Electronic Case Report Forms

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

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

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

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

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

9.9 Good Clinical Practices and Ethical Study Conduct

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

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

9.10 End of Study Notification

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

9.11 Publication of Results

All publications (e.g. manuscripts, abstracts, oral/slide presentations, book chapters) based on this study or relying on data from this study must be submitted to the Sponsor for review and

release before submission for publication. The Sponsor is responsible for final approval of all publications.

9.12 Final Report

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

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APPENDIX A SCHEDULE OF ACTIVITIES AND ASSESSMENTS

Table 2 Schedule of Visit Activities

Examination	Screening	Mid-Screening[TC]	Baseline[1]	Week 1[TC] (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 10 (± 7 days)	F/U[2]	Early Treatment Discontinuation
Demographics	X									
Informed consent	X									
WI-NRS[3]	X	X	X	X	X	X	X	X		
DLQI			X			X		X		X
HADS, ESS			X			X		X	X	X
ECG	X				X	X		X	X	X
Vital signs	X		X		X	X	X	X	X	X
Medical history (and prior medications)	X	X	X							
Physical exam[4]	X		X		X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X
Labs[5]	X				X			X	X	X
Urine pregnancy test[6]	X		X			X	X	X	X	X
PK blood draw					X	X		X		
Review of I/E criteria	X	X	X							
IGA PN-A and IGA PN-S			X		X	X		X	X	X
Photography (selected sites)			X					X	X	X
Dispense/review menstrual diary (if applicable)	X		X		X	X	X	X	X	X
Dispense/collect eDiary	X								X	X
eDiary review/compliance[7]		X	X	X	X	X	X	X	X	
Dispense and/or collect study drug			X		X	X	X	X		X
Review study drug compliance					X	X	X	X		
AEs/SAEs[8]	X	X	X	X	X	X	X	X	X	X

[TC]Telephone Contact: The Mid-Screening telephone contact should only occur for subjects who require a washout longer than 2 weeks, at least 15 days prior to the scheduled Baseline visit.

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

[2]The Follow-up (F/U) visit occurs 21-35 days (+ 7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early.

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

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

[5]Labs are ideally performed in the morning, particularly at visits with endocrine assessments (including Reproductive Endocrinology for females under 55 at age of consent) at Screening, Week 10 and Follow Up. Iron Studies, serum IgE and Serology labs are done only at Screening visit; endomysial antibody test and other optional studies only performed at Screening;

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

[7]See Table 3 for eDiary assessments

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

Table 3 Schedule of eDiary Assessments

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

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

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

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

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

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

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

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

APPENDIX C WORST ITCH NUMERIC RATING SCALE QUESTIONNAIRE

NRS for Itch Intensity

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

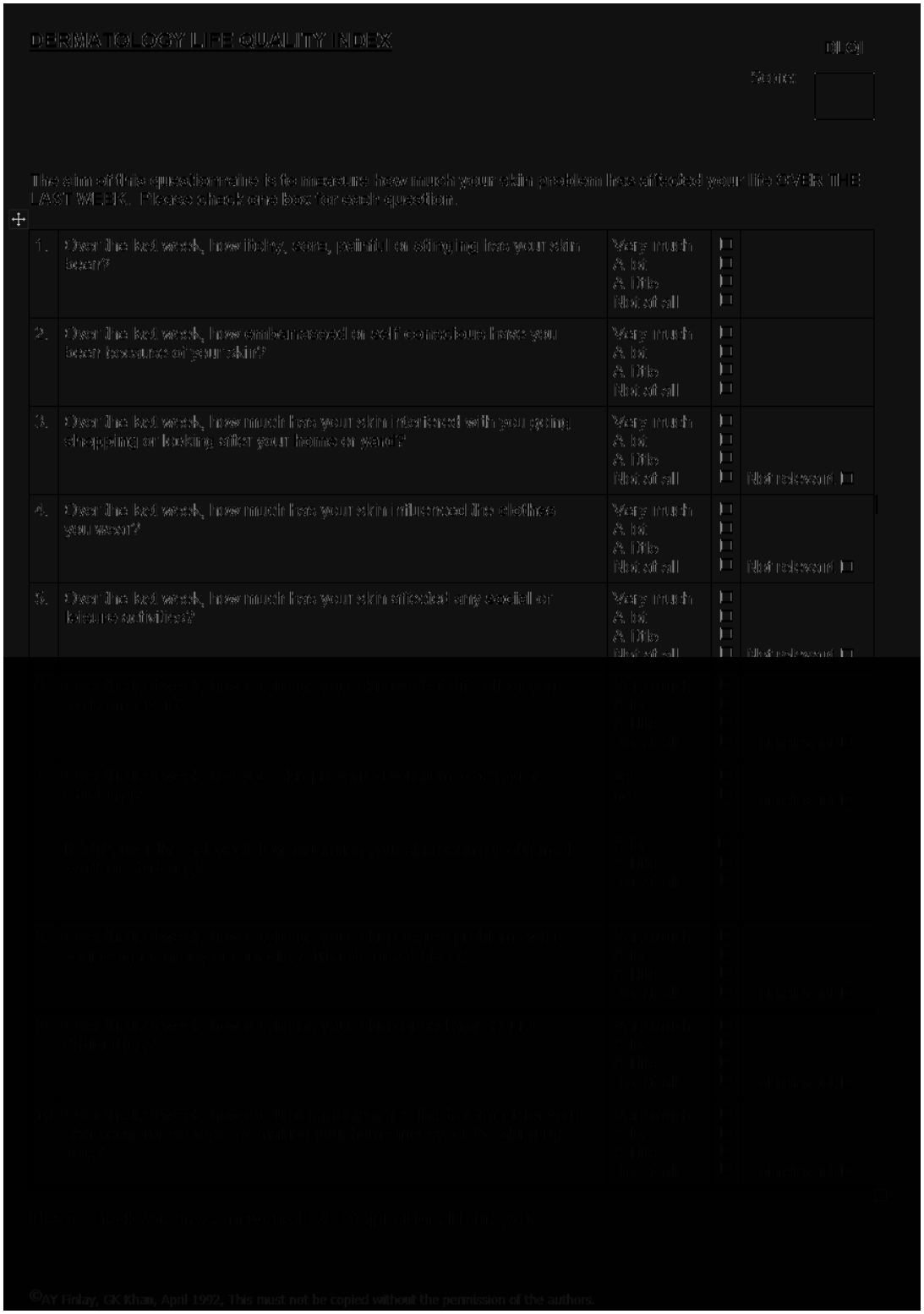
APPENDIX D INVESTIGATOR'S GLOBAL ASSESSMENT OF PRURIGO NODULARIS: ACTIVITY AND STAGE

Score	Category	Description: Activity (IGA PN-A)
0	**Clear**	No nodules have excoriations or crusts
1	**Almost Clear**	Very small proportion of nodules have excoriations or crusts (up to approximately 10% of all nodules)
2	**Mild**	Minority of nodules have excoriations or crusts (approximately 11- 25% of all nodules)
3	**Moderate**	Many nodules have excoriations or crusts (approximately 26- 75% of all nodules)
4	**Severe**	Majority of nodules have excoriations or crusts (approximately 76-100% of all nodules)

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

Name:

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 has 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 ☐

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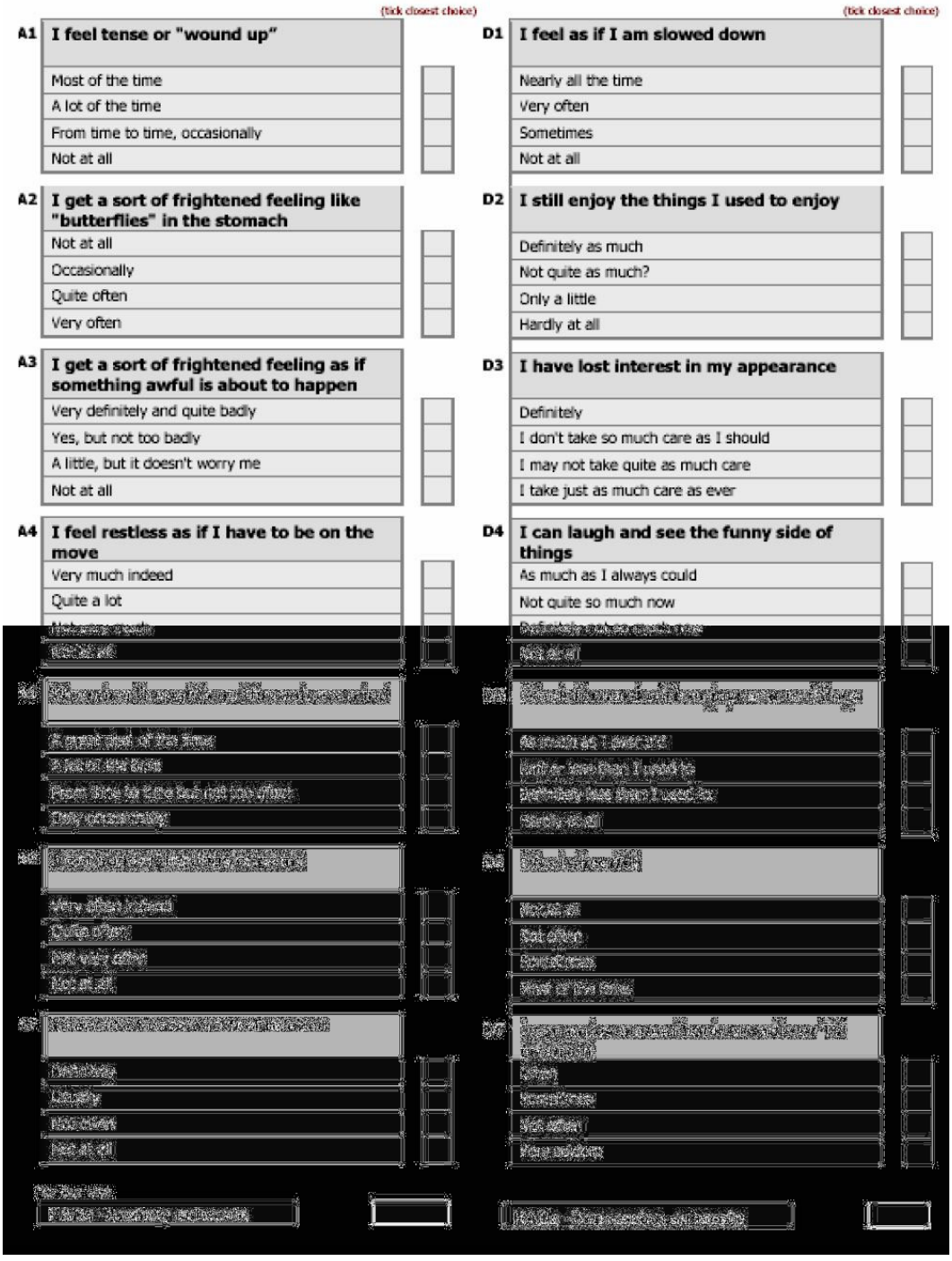
APPENDIX F HOSPITAL ANXIETY AND DEPRESSION SCALE



		(tick closest choice)			(tick closest choice)
A1	**I feel tense or "wound up"**		D1	**I feel as if I am slowed down**	
	Most of the time			Nearly all the time	
	A lot of the time			Very often	
	From time to time, occasionally			Sometimes	
	Not at all			Not at all	
A2	**I get a sort of frightened feeling like "butterflies" in the stomach**		D2	**I still enjoy the things I used to enjoy**	
	Not at all			Definitely as much	
	Occasionally			Not quite as much?	
	Quite often			Only a little	
	Very often			Hardly at all	
A3	**I get a sort of frightened feeling as if something awful is about to happen**		D3	**I have lost interest in my appearance**	
	Very definitely and quite badly			Definitely	
	Yes, but not too badly			I don't take so much care as I should	
	A little, but it doesn't worry me			I may not take quite as much care	
	Not at all			I take just as much care as ever	
A4	**I feel restless as if I have to be on the move**		D4	**I can laugh and see the funny side of things**	
	Very much indeed			As much as I always could	
	Quite a lot			Not quite so much now	

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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-106

SUMMARY OF CHANGES

Drug Product Name:	Serlopitant
Study Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
IND No.:	117780
EudraCT No.:	2017-004210-25
ClinicalTrials.gov ID:	NCT03677401
Protocol Version:	4.0
Protocol Date:	16 Dec 2019
Replaces Version/Date:	3.0 / 21 March 2019

The following changes were made to the MTI-106 Clinical Study Protocol from Version 3.0 to Version 4.0.

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.
3.3.2 Key Secondary Efficacy Endpoints	Removed 'Change from Baseline in Dermatology Life Quality Index (DLQI) to Week 10' Added 'WI-NRS 4-point responder rate at Week 2'	As a mixed tool consisting of 10 questions, not all of which are specific to subjects with pruritus, the DLQI may have limited utility in the subject population. It is therefore removed from the multiplicity testing strategy as a Key Secondary Efficacy Endpoint, however is still retained as an Additional Secondary Efficacy Endpoint to enable an evaluation of the potential improvement in quality of life (see below). An improvement in pruritus (≥4-point reduction in WI-NRS) may be realized as early as Week 2 of treatment and therefore is added as a Key Secondary Efficacy Endpoint and included in the multiplicity testing strategy.
3.3.3 Additional Secondary Efficacy Endpoints'	Removed 'WI-NRS 4-point responder rate at Week 2' Added 'Change from Baseline in DLQI to Week 10' Added 'Change from Baseline in DLQI Question 1 to Week 10'	Aligns with changes made to Section 3.3.2 Key Secondary Efficacy Endpoints, and retains ability to evaluate DLQI as an Additional Secondary Efficacy Endpoint Update due to prior change in SAP to analyze most relevant DLQI question as an additional secondary efficacy endpoint
8.1 Decision Rule and Sample Size	Removed 'Change from Baseline in DLQI to Week 10' Added 'WI-NRS 4-point responder rate at Week 2'	Aligns with changes made to Section 3.3.2 Key Secondary Efficacy Endpoints.
8.2 Handling of Missing Data	Changed the minimum number of observations needed to compute a week's average of WI-NRS from 1 observation to 4 observations. Removed the explanation for handling missing Week 10 DLQI data.	A requirement to use a minimum of 4 observations collected over the course of a week will better support computing a week's average for the WI-NRS, instead of allowing for use of a single data point.

Section(s)	Summary of Change	Reason for Change
	Updated the number of random seeds needed to impute missing data.	
8.8.2 Key Secondary Efficacy	Removed 'Change from Baseline in DLQI to Week 10' Added 'WI-NRS 4-point responder rate at Week 2' Removed information regarding the ANCOVA model	Aligns with changes made to Section 3.3.2 Key Secondary Efficacy Endpoints.
8.8.3 Additional Secondary Efficacy	Added information regarding the analysis of the secondary endpoints	Aligns with changes made to 3.3.3 Additional Secondary Endpoints
8.10.2 Clinical Safety Laboratory Results	Removed 'Graphs of laboratory values over time will also be produced.'	Update due to prior change in SAP

ADMINISTRATIVE CHANGES:

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

CLINICAL STUDY PROTOCOL

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
IND No.:	117780
Eudra CT:	2017-004210-25
ClinicalTrials.gov ID:	NCT03677401
Protocol No.:	MTI-106
Protocol Version/Date:	Version 4.0/16 December 2019
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063 USA

Confidentiality Statement:

SIGNATURE PAGE FOR PRINCIPAL INVESTIGATOR(S)

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
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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 Practices, and the Declaration of Helsinki.

_____
Principal Investigator's printed name

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

SPONSOR PROTOCOL APPROVAL SIGNATURE(S)

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF PRURITUS IN ADULTS WITH PRURIGO NODULARIS
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Protocol Version/Date:	Version 4.0/16 December 2019
Development Phase:	Phase 3
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063 USA

PPD

PROTOCOL SYNOPSIS

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Pruritus in Adults With Prurigo Nodularis
Protocol Number:	MTI-106
Sponsor:	Menlo Therapeutics Inc.
Development Phase:	Phase 3
Study Objectives:	Efficacy objective: To assess the efficacy of serlopitant for the treatment of pruritus in adults with prurigo nodularis. Safety objective: To assess the safety and tolerability of repeated oral doses of serlopitant in adults with prurigo nodularis.
Study Design:	This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with prurigo nodularis (PN). Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 3- or 5-week follow-up period. The study will consist of three periods, for a total study period of 15 to 19 weeks: • Screening period: 2-4 weeks • Treatment period: 10 weeks • Follow-up period: 3 or 5 weeks During the screening period, all subjects will undergo eligibility evaluation and will be assessed for chronic pruritic conditions frequently associated with PN. Subjects who present with idiopathic PN at screening may require additional assessments as deemed necessary by the investigator (e.g. endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis, skin biopsy for subjects with signs or symptoms of bullous pemphigoid or cutaneous T-cell lymphoma, urea breath test for *Helicobacter pylori*, or allergy testing). All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of electronic diary (eDiary) screening data. Subjects who require a screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit. Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study. At the Baseline visit (Day 1), eligible subjects will be randomly assigned to receive study drug (serlopitant 5 mg or placebo). Subjects will take a loading dose (3 tablets taken orally) at the site on the first day of the treatment period (Day 1). Starting on Day 2, subjects will take one tablet per day. Study drug may be taken with or without food.

	The primary efficacy endpoint will be assessed at Week 10 of treatment. Subjects who complete the 10-week treatment period and required follow-up period may be given the opportunity to enroll in a one-year open-label safety study with daily oral doses of serlopitant 5 mg.
Safety Review:	An internal safety monitoring team consisting of representatives from Menlo Therapeutics Inc. and its designees will monitor blinded safety data on a regular basis throughout the study.
Planned Sample Size:	Approximately 280 subjects will be randomized.
Study Population:	The study will consist of adult subjects with pruritus associated with PN. Inclusion Criteria (Subjects must meet the following criteria to be randomized into the study): 1. Male or female, age 18 years or older at consent. 2. A diagnosis of PN, defined by the presence of at least ten pruriginous nodules secondary to chronic pruritus present on at least two different body surface areas (e.g. both arms, one arm and one leg, one arm and the anterior trunk, or anterior and posterior trunk). 3. The worst pruritus is identified to be within the areas of the PN lesions. 4. Subject has idiopathic PN OR the subject has an identified pruritic condition associated with the PN and has persistent pruritus despite at least 6 weeks of optimized and stable treatment of the underlying condition prior to the Baseline visit, and is willing to continue the treatment during the study. 5. Worst-Itch Numeric Rating Scale (WI-NRS) score ≥ 7 in the 24-hour period prior to the Screening visit. 6. Average weekly WI-NRS score ≥ 6.5 in each of the 2 weeks (14 days) immediately prior to Baseline visit, as recorded in the eDiary. 7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last dose of study drug. 8. Willing and able (as demonstrated by a ≥ 70% eDiary completion rate in the two weeks prior to Baseline visit) to complete daily eDiary entries within a consistent timeframe for the duration of the study. 9. 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. Prior treatment with serlopitant. 2. Active pruritic skin disease, other than PN, within 6 months prior to randomization (with the exception of acute dermatoses such as contact dermatitis, sunburn, viral exanthem, which have been resolved for longer than 4 weeks). 3. Treatment with any of the following therapies within 4 weeks prior to randomization.

	a. Other neurokinin-1 receptor antagonists (e.g., aprepitant, fosaprepitant, rolapitant). b. Systemic or topical immunosuppressive/immunomodulatory therapies (including but not limited to corticosteroids, phosphodiesterase-4 inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, interferon-gamma, thalidomide, or phototherapy). c. Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists (e.g. naloxone, naltrexone)). d. Strong cytochrome-P 3A4 inhibitors. e. Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn. 4. Treatment with topical anti-pruritic therapies (e.g., menthol, camphor, pramoxine, capsaicin) within 2 weeks prior to randomization. 5. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer. 6. Treatment with any investigational therapy within 4 weeks (8 weeks for investigational biologic therapies) or 5 half-lives prior to randomization, whichever is longer. 7. Serum creatinine, total bilirubin, alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal during screening. 8. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease, or history of thyroid malignancy. 9. History of malignancy within 5 years prior to randomization, with the exception of actinic keratosis, completely treated and non-metastatic cutaneous basal cell carcinoma or squamous cell carcinoma of the skin. 10. 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 randomization. 11. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt. 12. Documented history of parasitic infection, including skin parasites such as scabies, within 8 weeks prior to randomization. 13. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject. 14. History of hypersensitivity to serlopitant or any of its components. 15. Currently pregnant or breastfeeding female subject. 16. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated

	assessments (e.g. extended international travel) during the subject's participation in the study.
Study Drug:	Serlopitant 5 mg oral tablets and matching placebo.
Dosage:	Serlopitant: 5 mg once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period. Matching placebo: Once daily by mouth for 10 weeks, following a 3-tablet loading dose on the first day of the treatment period.
Primary Efficacy Endpoint:	The primary efficacy endpoint is the WI-NRS 4-point responder rate at Week 10.
Secondary Efficacy Endpoints:	The key secondary efficacy endpoints are as follows: • WI-NRS 4-point responder rate at Week 4 • WI-NRS 4-point responder rate at Week 2 Additional secondary efficacy endpoints are as follows: • Change from baseline in WI-NRS to other timepoints • WI-NRS 3-point responder rate at Weeks 2, 4 and 10 • Change from baseline in Dermatology Life Quality Index (DLQI) to Week 10 • Change from baseline in DLQI Question 1 to Week 10 • Change from baseline in Investigator's Global Assessment of PN Activity to Weeks 2, 4 and 10 • Change from baseline in Investigator's Global Assessment of PN Stage to Weeks 2, 4 and 10
Safety Endpoints:	Safety endpoints are as follows: • Incidence of treatment-emergent adverse events and serious adverse events (SAEs) • Changes from baseline in clinical laboratory parameters following study drug exposure • Changes from baseline in vital sign and electrocardiogram (ECG) parameters following study drug exposure • Changes from baseline in the Hospital Anxiety and Depression Scale (HADS) • Changes from baseline in the Epworth Sleepiness Scale (ESS)
Decision Rule and Sample Size:	This study will use a 5% two-sided alpha level. Hierarchical testing in which statistical significance for the key secondary efficacy endpoints requires statistical significance for the primary endpoint. The target sample size of 280 randomized and dosed subjects (140 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. Completed Phase 2 studies indicate that placebo responder rates vary between CCI% and CCI% and serlopitant rates between CCI% and CCI%. A sample size of 280 subjects provides >90% power assuming a placebo responder rate of CCI% and a serlopitant rate of CCI%.
Statistical Methods:	Efficacy analyses will be based upon an intent-to-treat philosophy. The primary

	efficacy population will be the Intent-to-Treat (ITT) population that will include all randomized subjects who were dispensed study drug. Analyses performed on the Per Protocol population will be considered supportive. Subjects will be analyzed within the treatment group to which they are randomized. Efficacy Analyses: The primary efficacy endpoint is a binary variable taking on values of responder or non-responder. Subjects will be considered a responder if they have at least a 4-point reduction in WI-NRS between baseline and Week 10. Missing data imputation will be used for subjects who fail to complete the eDiary at Week 10, unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. The primary endpoint will be summarized with descriptive statistics by treatment group and study week. The difference in the primary efficacy outcome measure between treatment groups will be tested using a Cochran Mantel Haenszel test controlling for the stratification factors. Testing of the key secondary efficacy endpoints will also be employed.
	Safety Analyses: The incidence of all adverse events (AEs) and treatment-related AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. An overview of AEs, which includes subject incidence of AEs, treatment-related AEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented. Clinical safety laboratory values will be measured by a central laboratory. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Subjects with clinical laboratory values outside of the normal reference range at any post-baseline assessment will be summarized. Shifts from baseline laboratory values will be tabulated. The overall ECG assessment (abnormal or normal) will be summarized along with a summary of how many subjects developed a post treatment abnormal result. Summary statistics for the HADS and ESS actual values and change from baseline will be presented by scheduled visit.
Study Sites:	Approximately 50 study sites.
Expected Duration of Subject's Participation	15-19 weeks: 2-4 weeks of screening, 10 weeks of treatment, and a follow-up period of 3 or 5 weeks.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone, corticotropin
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CMH	Cochran Mantel Haenszel test
CNS	Central Nervous System
CRO	Contract Research Organization
CYP3A4	Cytochrome-P 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ESS	Epworth Sleepiness Scale
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAART	Highly active antiretroviral therapy
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA PN-A	Investigator's Global Assessment of Prurigo Nodularis Activity
IGA PN-S	Investigator's Global Assessment of Prurigo Nodularis Stage
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
LFC	Liquid filled capsule
LH	Luteinizing hormone
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor

NOAEL	No observed adverse effect level
NRS	Numeric Rating Scale
PET	Positron Emission Tomography
PI	Principal Investigator
PD	Pharmacodynamics
PDE-4	Phosphodiesterase-4
PK	Pharmacokinetics
PN	Prurigo nodularis
PP	Per Protocol
QOL	Quality of life
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Substance P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WI-NRS	Worst-Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Pruritus in Prurigo Nodularis

Prurigo nodularis (PN) is a distinctive and easily diagnosable chronic skin condition characterized by the presence of multiple highly pruritic and often symmetrically distributed nodules and papules on the skin (Jorizzo 1981). The nodules and papules in PN can range in size from approximately 0.5 to 3.0 cm and often appear hyperkeratotic, sometimes crateriform, in appearance. Plaques are occasionally present, and the lesions of PN frequently exhibit other features secondary to prolonged and severe scratching behavior, such as post-inflammatory hyperpigmentation, erosion, ulceration, crusting, and bleeding (Zeidler 2016).

PN, a long-term reaction to the chronic scratching and picking of patients with chronic pruritus (Zeidler 2016), is a skin condition seen predominantly in older adults, with median prevalence age in the 50s and 60s and a slight female preponderance (Iking 2013, Tan 2014, Ständer 2013). In one patient population survey, pediatric patients accounted for <2% of the total population, with the youngest patient 11.9 years of age (Iking 2013). Although only limited epidemiology data for PN have been published, a claims-based analysis commissioned by Menlo Therapeutics suggest that the United States (US) prevalence may be in the range of ~ 355,000 affected individuals. Based on a quantitative survey of 73 dermatologists conducted in parallel with the claims-based analysis, approximately 23% of patients with PN have an underlying atopy-related condition, while over 50% are considered to be idiopathic (Navigant 2017). The median duration of disease burden has been reported to be 6-7 years (Iking 2013, Tan 2014, Schuhknecht 2011).

The dominant symptom in PN is an intense and chronic pruritus that is associated with a high degree of patient burden and restricted quality of life (QOL) (Zeidler 2016). As measured by global scales of pruritus intensity (numeric rating scale (NRS) and visual analog scale (VAS)), median levels of pruritus intensity have been reported to be 7-8 points (Iking 2013, Tan 2014, Schuhknecht 2011). The pruritus experienced in PN can often prevent patients from adequately performing their daily activities (Vaidya 2008), and patients with PN have been found to suffer from greater rates of depression and anxiety than control groups in numerous studies (Jorgensen 2016, Rowland Payne 1985, Dazzi 2011).

1.2 Conditions Associated With Prurigo Nodularis

As PN is considered to be a disease induced by chronic pruritus and ongoing scratching activity, a variety of chronic pruritic conditions have been identified as potential underlying etiologies for the pruritus, including atopic dermatitis (AD), other inflammatory or bullous skin diseases, chronic renal failure, human immunodeficiency virus (HIV) infection, hepatitis C infection, and multifactorial disease (i.e. two or more co-existent conditions associated with chronic pruritus) (Fostini 2013, Lee 2005). The mechanisms linking chronic pruritus to the development of PN are not clear, as only a subset of patients with chronic pruritus develop PN, and over half of patients with PN have no underlying etiology identified. Even when specific underlying conditions are identified, management of these condition(s) does not usually result in resolution of PN signs or symptoms, nor can all underlying conditions be treated. For example, PN has been observed in patients with HIV adequately managed with

highly active antiretroviral therapy (HAART) (Zancanaro 2006), in patients with intractable cholestatic pruritus (Bergasa 2011), in patients with inactive hepatitis (Halvorsen 2015), and commonly in patients with renal failure despite hemodialysis therapy (Goeksel 2013). These data point to a high level of unmet medical need in the overall PN population, as the majority of patients with PN either have no underlying condition identified that can be treated, or treatment of the underlying condition is inadequate to control their PN (Wallengren 2004).

1.3 Current Treatment Options for Prurigo Nodularis

Treatment of PN remains a challenging and extremely frustrating experience for both patients and physicians. In the majority of cases, responses are limited and unsatisfactory, and once the cycle of pruritus-excoriation-pruritus begins, it is difficult to stop. Identification and treatment of underlying chronic pruritic conditions is often the first step in management of PN. If this does not result in resolution of the pruritus, or if no underlying condition is identified, treatment specifically for PN and its associated pruritus is implemented.

First-line pruritus therapies, including topical agents such as topical corticosteroids and calcineurin inhibitors, often provide inadequate response (Saco 2015) and the therapeutic ladder for PN involves systemic agents with progressively riskier safety profiles. These include naltrexone, gabapentin, mirtazapine, phototherapy, intravenous immunoglobulin (IVIG), powerful immunosuppressants such as methotrexate and cyclosporine, and thalidomide (Ständer 2015b, Spring 2014, Feldmeyer 2012, Lim 2016). None of these therapies are indicated for the treatment of PN, and their usage is often based on limited evidence, such as case reports or small open-label studies.

1.4 Substance P and the Neurokinin-1 Receptor

Repeated itching, scratching, and picking over long time periods serve as the pathophysiological basis for the development of PN. Although different underlying disease states may be responsible for the chronic pruritus, the distinctive and easily recognizable features of PN point to a common final pathway resulting in this unique clinical presentation.

Immunohistochemical staining studies of PN biopsies have demonstrated that nerve fibers immunoreactive for Substance P (SP) are found in increased numbers in lesional skin compared to non-lesional skin or controls (Abadía Molina 1992), suggesting a role for SP signaling in PN. These findings are consistent with the robust body of evidence indicating the key role of SP signaling through its primary receptor, the neurokinin-1 receptor (NK_1-R), in the transmission of itch across multiple disease states (Santini 2012, Akiyama 2015, Crowe 1994, El-Nour 2006, Lotts 2014, Hon 2007, Ward 2004, Slattery 2011).

SP is an undecapeptide that belongs to the tachykinin family of neuropeptides, a group that also includes neurokinin A and neurokinin B (Hökfelt 2001). SP has been implicated in a number of biological functions, both physiological and pathophysiological, including pruritus perception, vomiting reflex, pain perception, and immunomodulatory responses (Lotts 2014, Andoh 1998, Steinhoff 2014). The biological actions of SP are mediated by tachykinin receptors, which consist of seven hydrophobic transmembrane domains coupled to G-proteins. Three tachykinin receptors have been identified: the neurokinin-1, neurokinin-2,

and neurokinin-3 receptors (Harrison 2001). The NK_1-R 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, include central and peripheral neurons, keratinocytes, and mast cells.

NK_1-R stimulation has been shown to be an important pathway for pruritus perception (Ständer 2015a). 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).

1.5 Serlopitant

1.5.1 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.

1.5.2 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 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.

1.5.3 Serlopitant in Pruritus-Related Studies

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

TCP-101

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

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

squares mean difference compared to placebo was 5.8 mm, 13.2 mm, and 14.2 mm for serlopitant 0.25 mg, 1 mg, and 5 mg, respectively.

The frequency of 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.

Potential Risks and Benefits: 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 treatment of pruritus in patients with PN. The potential benefits of continued clinical study outweigh the potential risks.

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

2 STUDY OBJECTIVES

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

The safety objective of this study is to assess the safety and tolerability of repeated oral doses of serlopitant in adults with PN.

3 STUDY DESIGN

3.1 Overall Study Design

This is a double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in adults with PN. The study will be conducted at approximately 50 study sites. Subjects who meet the study entry criteria will be randomized in a 1:1 ratio to receive daily oral doses of serlopitant 5 mg or placebo for 10 weeks. After completion of the treatment period or early discontinuation of study drug treatment, all subjects will enter a 3 or 5-week follow-up period. The required follow-up period is defined as a minimum of 3 weeks for those subjects who will enroll in the one-year open-label safety study (MTI-107) on the date of the follow-up visit, and as 5 weeks for those subjects who will not be enrolled in the one-year open-label safety study of serlopitant. Should a subject present for the follow-up visit prior to 5 weeks after the last dose of study drug and be excluded from participation in the one-year study for any reason, the subject will be required to return at 5 weeks after the last dose of study drug for a complete follow-up visit.

This study will consist of three periods, for a total study period of 15-19 weeks:

- Screening period: 2-4 weeks
- Treatment period: 10 weeks
- Follow-up period: 3 or 5 weeks

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

During the screening period, all subjects will undergo eligibility evaluation and will be assessed for chronic pruritic conditions frequently associated with PN. Subjects who present with idiopathic PN at screening may require additional assessments as deemed necessary by the investigator (e.g. endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis, skin biopsy for subjects with signs or symptoms of bullous pemphigoid or cutaneous T-cell lymphoma, urea breath test for *Helicobacter pylori*, or allergy testing).

All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of electronic diary (eDiary) screening data. Subjects who require screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred following discussion with the medical monitor should more than 31 days be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition).

Screening procedures may be repeated (i.e., the subject may be rescreened) following discussion with the medical monitor should the subject have had difficulty complying with eDiary assessments, require further training in the assessments, or have other relevant needs that may delay enrollment in the study but are not expected to impact safety or efficacy assessments.

Subjects will be provided an eDiary at the Screening visit. Subjects must be willing and able to complete the eDiary every day within a consistent timeframe, and comply with restrictions on allowable concomitant therapies, for the duration of the study.

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

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

Subjects who complete the 10-week treatment period and required follow-up period may be given the opportunity to enroll in a one-year open-label safety study (MTI-107) with daily oral doses of serlopitant 5 mg.

3.2 Rationale for Study Design and Dose Selection

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

superior to placebo for the reduction of pruritus, in both the overall study population and the subgroup of subjects with an atopic diathesis.

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

The current MTI-106 study is designed to confirm the efficacy, safety, and tolerability of serlopitant for the treatment of pruritus in patients with PN. 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. Over 250 subjects have been exposed to serlopitant at doses of 5 mg tablet-equivalent daily for at least 6 weeks, and ~ 40 subjects have been exposed up to one year. Human CNS PET RO data for serlopitant in healthy young males (Study P002) demonstrated that a serlopitant 5 mg LFC once daily dose is likely to achieve ~ 94% NK_1 RO at steady state.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

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

3.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- WI-NRS 4-point responder rate at Week 4
- WI-NRS 4-point responder rate at Week 2

3.3.3 Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints are as follows:

- Change from baseline in WI-NRS to other timepoints
- WI-NRS 3-point responder rate at Weeks 2, 4 and 10
- Change from baseline in Dermatology Life Quality Index (DLQI) to Week 10
- Change from baseline in DLQI Question 1 to Week 10
- Change from baseline in Investigator's Global Assessment of PN Activity (IGA PN-A) to Weeks 2, 4 and 10
- Change from baseline in Investigator's Global Assessment of PN Stage (IGA PN-S) to Weeks 2, 4 and 10

3.3.4 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs and SAEs
- Change from baseline in clinical laboratory parameters following study drug exposure
- Change from baseline in vital sign and 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)

3.4 Safety Review

3.4.1 Safety Monitoring Team

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

4 SELECTION OF STUDY POPULATION

4.1 Study Population

Approximately 280 adult subjects with pruritus associated with PN will be enrolled in this study.

4.2 Inclusion Criteria

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

1. Male or female, age 18 years or older at consent.
2. A diagnosis of PN, defined by the presence of at least ten pruriginous nodules secondary to chronic pruritus present on at least two different body surface areas (e.g. both arms, one arm and one leg, one arm and the anterior trunk, or anterior and posterior trunk).
3. The worst pruritus is identified to be within the areas of the PN lesions.
4. Subject has idiopathic PN OR the subject has an identified pruritic condition associated with the PN and has persistent pruritus despite at least 6 weeks of optimized and stable

treatment of the underlying condition prior to the Baseline visit, and is willing to continue the treatment during the study. Please refer to Section 5.7.1.

5. WI-NRS score ≥ 7 in the 24-hour period prior to the Screening visit.
6. Average weekly WI-NRS score ≥ 6.5 in each of the 2 weeks (14 days) immediately prior to Baseline visit, as recorded in the eDiary.
7. All female subjects who are of childbearing potential must be willing to practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the Screening visit until 5 weeks after last dose of study drug. Please refer to Section 7.1.5 for acceptable methods of contraception.
8. Willing and able (as demonstrated by a ≥ 70% eDiary completion rate in the two weeks prior to Baseline visit) to complete daily eDiary entries within a consistent timeframe for the duration of the study.
9. 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. Prior treatment with serlopitant.
2. Active pruritic skin disease, other than PN, within 6 months prior to randomization (with the exception of acute dermatoses such as contact dermatitis, sunburn, viral exanthem, which have been resolved for longer than 4 weeks). Please refer to Section 5.7.1.
3. Treatment with any of the following therapies within 4 weeks prior to randomization.
    a. Other NK_1-R antagonists (e.g., aprepitant, fosaprepitant, rolapitant).
    b. Systemic or topical immunosuppressive/immunomodulatory therapies (including but not limited to corticosteroids, phosphodiesterase-4 (PDE-4) inhibitors, cyclosporine, mycophenolate-mofetil, tacrolimus, pimecrolimus, calcipotriene, methotrexate, azathioprine, interferon-gamma, thalidomide, or phototherapy).
    c. Systemic therapies with recognized anti-pruritic properties (including but not limited to H1 antihistamines, doxepin, gabapentin, pregabalin, cannabinoids, kappa-opioid receptor agonists, and mu-opioid receptor antagonists (e.g. naloxone, naltrexone)).
    d. Strong CYP3A4 inhibitors (see Appendix B).
    e. Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn.
4. Treatment with topical anti-pruritic therapies (e.g., menthol, camphor, pramoxine, capsaicin) within 2 weeks prior to randomization (see Section 5.7.2).

5. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to randomization, whichever is longer.
6. Treatment with any investigational therapy within 4 weeks (8 weeks for investigational biologic therapies) or 5 half-lives prior to randomization, whichever is longer.
7. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) during screening.
8. Untreated or inadequately treated thyroid, adrenal, or pituitary nodules or disease or history of thyroid malignancy.
9. History of malignancy within 5 years prior to randomization, with the exception of actinic keratosis, completely treated and non-metastatic cutaneous basal cell carcinoma or squamous cell carcinoma of the skin.
10. 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 randomization.
11. Suicidal ideation within 3 years prior to randomization, or any history of suicide attempt.
12. Documented history of parasitic infection, including skin parasites such as scabies, within 8 weeks prior to randomization.
13. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject.
14. History of hypersensitivity to serlopitant or any of its components.
15. Currently pregnant or breastfeeding female subject.
16. Planned or anticipated major surgical procedure or other activity that would interfere with the subject's ability to comply with protocol-mandated assessments (e.g. extended international travel) during the subject's participation in the study.

5 STUDY DRUG

5.1 Study Drug Supply, Route of Administration, and Storage

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

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

The tablets will be supplied in bottles, with 18 tablets per bottle. One bottle will be issued via Interactive Web Response System (IWRS) at baseline and at Weeks 2 and 4, and two bottles will be issued via IWRS at Week 6. A total of 5 bottles will be dispensed to subjects completing 10 weeks of study drug treatment.

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

5.2 Labeling and Study Drug Accountability

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

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

5.3 Dosing Regimen

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

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

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

5.6 Study Drug Discontinuation

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

- A female subject desires to become pregnant at the current time, stops contraception or expels her intrauterine device/implant, or becomes pregnant
- A female subject has new breast findings (e.g. a palpable mass or abnormal mammography, discharge), or has abnormal vaginal discharge or bleeding
- The subject decides to discontinue study drug treatment, or withdraws consent from the study
- The subject receives a strong CYP3A4 inhibitor (See Appendix B)

- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion; this may include the development of persistently (2 successive occasions) abnormal thyroid function tests (TSH >10, or TSH > 6 with low free T4; TSH <0.1, or TSH < 0.35 with high free T4); abnormal morning prolactin, cortisol, or corticotropin levels; or signs and symptoms of adrenal insufficiency
- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion, including evidence that the subject does not meet inclusion/exclusion criteria intended primarily for safety reasons, or a persistent lack of adherence to study procedures

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

Subjects who discontinue treatment with study drug prior to completing the treatment period will enter a 5-week follow-up period following the last dose of study drug in addition to a Follow-up visit (see Section 3.1, Section 6.5.10). Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued from study drug.

5.7 Prior, Concomitant, and Excluded Therapies

Prior therapies (including over-the-counter medications) used to treat the signs and symptoms of PN within the prior 2 years will be recorded for each subject at the Baseline visit.

Concomitant therapies include any therapies (including over-the-counter medications and bland emollients) used by a subject from initiation of study drug treatment through the follow-up period. A record of all medications used will be maintained for each subject throughout the study. Reported information will include a description of the type of drug, treatment period, dosing regimen, the route of administration, and drug indication. The use of any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements, emollient use, and routine preventative immunizations.

5.7.1 Allowed Therapies and Treatment Goals for Underlying Conditions

Treatment of an underlying, treatable chronic pruritic condition is allowed, if stable for at least 6 weeks prior to the Baseline visit, and continued throughout the treatment period.

Treatment of the underlying systemic pruritic condition should be optimized per standard of care and treatment goals must be tailored based on age, sex, and concurrent health status and drug tolerance. While resolution of metabolic or endocrine disorders or eradication of an underlying infection may not always be feasible, every effort should be made to ensure the condition is well controlled, to prevent or reduce exacerbations and to prevent limitation on the activities of daily living. When applicable, laboratory evidence of control should be obtained. For example, if renal insufficiency is implicated as causal for pruritus, treatment

would be expected to have meaningfully reduced the creatinine (compared to that at the time of diagnosis) and to maintain the creatinine at < 2.5 the ULN; control of diabetes is supported by a hemoglobin-A1c of < 7.5%; control of thyroid disease is supported by normalization of the thyroid stimulating hormone (TSH) or by a TSH within 1.5 times the ULN in elderly patients; iron deficiency is corrected with a serum iron within 0.8 times the lower limit of normal; eradication of *Helicobacter pylori* infection generally requires a negative urea breath test and fecal antigen test and endoscopy; and the viral load should be undetectable if viral infections such as hepatitis B or hepatitis C, or HIV were previously diagnosed. Any previously active skin disease is considered to be well controlled if it is globally considered clear or almost clear (permissible to have post-inflammatory pigmentation, fine scale, faint pink erythema, barely perceptible induration/papulation, and no oozing or crusting).

Use of gentle cleansers and bland emollients (including those with urea) is encouraged for all subjects. If bland emollient use is elected, it must be initiated at least 2 weeks (14 days) prior to Baseline visit, and continued throughout the treatment period.

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

Leukotriene inhibitors will be permitted for treatment of conditions other than PN (e.g. asthma).

5.7.2 Excluded Therapies

Initiation or use of topical therapy with corticosteroids, calcineurin inhibitors, calcipotriene, PDE-4 inhibitors is not permitted within 4 weeks prior to the Baseline visit or throughout the treatment period, but such therapy may be initiated during the follow-up period if needed.

Initiation of bland emollient is not permitted within 2 weeks (14 days) prior to Baseline visit or throughout the treatment period, but such therapy may be initiated during the follow-up period if needed.

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

- NK_1-R antagonists (other than study drug)
- Systemic immunosuppressive/ immunomodulatory therapies (including but not limited to systemic corticosteroids, PDE-4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, thalidomide, interferon-gamma, or phototherapy)
- Biologic therapies (other than therapies such as insulins, vaccines)
- Strong CYP3A4 inhibitors (See Appendix B)
- Use of an indoor tanning facility, or natural sun exposure resulting in significant tanning or sunburn
- Any investigational therapy

The following therapies and activities are excluded from the Screening visit through the treatment period, and use is discouraged, though permitted, through the follow-up period:

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

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

5.7.3 Rescue Therapies

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

5.8 Assignment to Treatment

5.8.1 Randomization

Eligible subjects will be randomized to receive serlopitant 5 mg or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by the subject's reported WI-NRS score for the 1-week period prior to the Baseline visit (6.5 to < 9, 9 to 10).

An IWRS will be used to perform the randomization.

5.8.2 Blinding

This study will be conducted as a double-blind study with the treatment assignment concealed from the subjects, the investigators and their staff, the Sponsor, and any designees of the Sponsor as required. The placebo will be formulated to be indistinguishable from the active study product. Study materials will be packaged and issued in a manner designed to maintain the blind for subjects and all study personnel involved in the direction and execution of study procedures, study assessments, and collection of data. The randomization code for each subject will be available to the sites for use only in an emergency situation. For details of the procedure for unblinding of individual subjects in cases of emergency see Section 7.6.

5.9 Treatment Compliance

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

6 STUDY SCHEDULE AND ASSESSMENTS

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

6.1 Efficacy Parameters

6.1.1 Itch Numeric Rating Scale

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

6.1.2 Investigator's Global Assessment of PN Activity

The IGA PN-A is an instrument used to assess the overall activity 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-A uses clinical characteristics of excoriations, crusting, and/or bleeding as guidelines for the overall activity assessment. The number of pruriginous lesions should not be considered for this assessment. IGA PN-A scores will be captured as outlined in 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 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 of number of nodules and their thickness as guidelines for the overall severity assessment. IGA-PN-S scores will be captured as outlined in Appendix A. Each assessment during the study must be done by the 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.

6.1.4 Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI) is a dermatology specific QOL instrument designed to assess the impact of the skin disease on a subject's QOL over the prior week. It is a ten-item questionnaire that assesses overall 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 outlined in Appendix A.

6.1.5 PN Photographs

At selected investigative sites, optional photographs of representative areas with PN involvement will be taken at multiple time points, as outlined in 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. The PI and designees will be trained on the use of the camera and the appropriate lighting and positioning of the representative area with PN involvement. Detailed instructions will be provided in the 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 as outlined in Appendix A.

6.2.1 Vital Signs

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

6.2.2 Physical Examination

Physical examinations, including height and weight measurements, will be performed as outlined in Appendix A and at unscheduled study visits when clinically indicated. A complete physical examination will be performed at the screening visit, while subsequent examinations will be abbreviated and targeted to changes in disease activity and/or subjects' symptoms. 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 outlined in Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified.

Detailed instructions regarding sample collection, preparation, and shipment can be found in the laboratory manual. Laboratory assessments will include the following, and are ideally performed in the morning, particularly at visits with endocrine assessments (Screening, Week 10, Follow-up):

- Hematology: hematocrit, hemoglobin, red blood cell count, red blood cell indices, platelets, white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, albumin, uric acid, total protein, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), lipid panel
- Iron studies: ferritin, serum iron
- Serology: hepatitis B and C serology, HIV
- Serum IgE
- Pregnancy testing: all females of childbearing potential will have a local urine pregnancy test performed. Positive or equivocal urine pregnancy test results will be confirmed by a serum pregnancy test analyzed at a central laboratory
- Endocrine: TSH, free T4, cortisol, corticotropin (adrenocorticotropic hormone, ACTH), prolactin
- Reproductive endocrinology (for all female subjects under 55 years of age at consent): serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Mullerian hormone (AMH)
- Optional study provided in lab test kits for use at Screening only: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis

- Additional optional studies will be supported through local procedural and/or laboratory assessments, including, but not limited to, 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.
- Standard cosyntropin stimulation testing should be performed on subjects with low cortisol level (i.e. < 3.0 mcg/dL); the investigator should discuss low cortisol (and relevant low corticotropin) results with the medical monitor.

6.2.4 Electrocardiogram

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

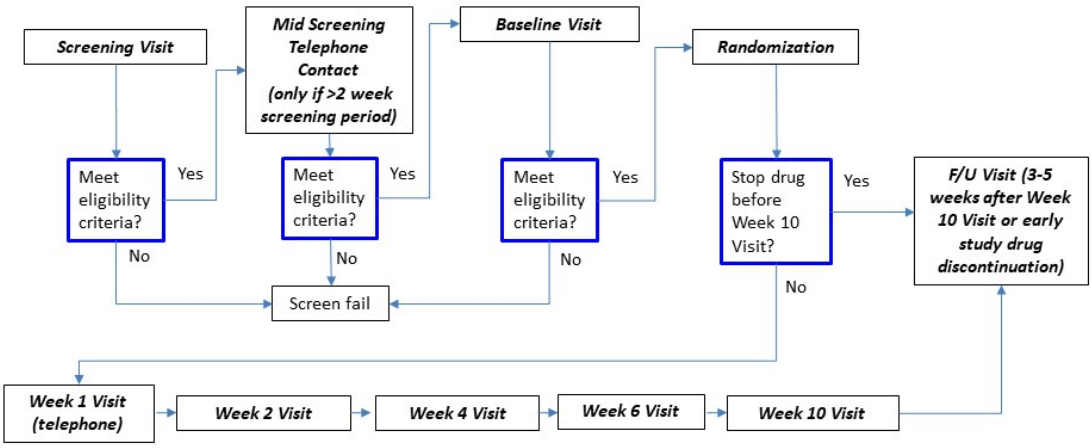
6.3 Pharmacokinetic Measurements

Sparse PK sampling will involve collecting one PK sample at each of the Week 2, Week 4, and Week 10 visits as outlined in Appendix A. The date and time of dosing prior to PK sample collection and date and time of PK sample collection will be collected. The plasma concentrations of serlopitant and metabolites will be determined and data used for population PK analysis. Detailed instructions regarding PK sample collection, preparation, and shipment can be found in the laboratory manual.

6.4 Subject Flow Diagram

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

Figure 1 Subject Flow Diagram



6.5 Study Visits

The following sections describe the procedures and assessments to be performed at each study visit. Details of each procedure and assessment can be found in Sections 6.1, 6.2, and 6.3. The timing of each study visit is relative to the day of randomization (Baseline).

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

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

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

6.5.1 Screening Period

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

All screening procedures must be completed within 31 days before the Baseline visit. The minimum screening period for all subjects is 14 days to allow for collection of eDiary screening data. Subjects who require screening period longer than 14 days will have a telephone contact at least 15 days prior to the scheduled Baseline visit to remind them to complete the eDiary as previously instructed at the Screening visit.

Screening procedures may be deferred following discussion with the medical monitor should more than 31 days be required (e.g. to wash out of certain excluded therapies or to treat their underlying condition).

Screening procedures may be repeated (i.e., the subject may be rescreened) following discussion with the medical monitor should the subject have had difficulty complying with eDiary assessments, require further training in the WI-NRS assessments, or have other relevant needs that may delay enrollment in the study but are not expected to impact safety or efficacy assessments.

6.5.2 Screening Visit

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

- Obtain written informed consent prior to any protocol-mandated procedures, including the stopping of any excluded therapies
- Collect demographic information (sex, date of birth, race, ethnicity)
- Ask subject to complete the WI-NRS scale on paper
- Register Screening visit into the IWRS
- Obtain ECG
- Obtain vital signs
- Review subject's medical history (including prior medications)
    - Record only significant/relevant medical history, to include the onset date of PN (as specifically as known) and presence of an underlying condition (if any)
    - Designate the primary and any concurrent medical conditions that are identified as pruritic conditions underlying the PN
    - 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) and confirm clinical diagnosis of PN
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
  - Serology
  - Serum IgE
  - Iron studies
  - Optional: endomysial antibody with reflex to titer for subjects with signs or symptoms of dermatitis herpetiformis
  - Optional: additional assessments (refer to Section 6.2.3)
- Review subject's tentative eligibility according to the Inclusion/Exclusion criteria
  - The results of all screening evaluations, including laboratory and ECG results, must be reviewed for clinical significance by the PI or designee, and may require further evaluation, prior to randomization of the subject on Baseline visit
- Schedule the Baseline visit and all future study visits to ensure subject's availability and visit compliance with the protocol visit windows
- Provide a menstrual diary to female subjects who report periodic menstruation
- Provide eDiary with instructions
- Confirm next scheduled visit

6.5.3 Mid-Screening Telephone Contact (for subjects longer than 14 days in Screening)

During this telephone contact the following procedures are to be performed:

- Assess and record any changes in medications since the Screening visit
- Review subject's tentative eligibility according to Inclusion/Exclusion criteria
- Assess AEs and record SAEs caused by protocol-mandated interventions

- Review eDiary for compliance, re-train subject as needed
- Confirm next scheduled visit

6.5.4 Baseline Visit

The Baseline visit occurs between 14 to 31 days after the screening visit, depending on the required washout period following discontinuation of excluded therapies. Eligibility must be confirmed prior to randomization. At the Baseline visit, the following procedures and assessments are to be performed, preferably in the order shown below:

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Assess and record any changes in the subject's medical history
  - Female subjects should be queried regarding history of, or current, breast masses or abnormal discharge, and history of mammography (if applicable), and history of abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Assess AE's and record SAEs caused by protocol-mandated interventions
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential and confirm the subject has a negative urine pregnancy test result prior to randomization (with positive or equivocal results confirmed by a serum pregnancy test)
- Confirm subject's eligibility based on the inclusion/exclusion criteria (to include review of eDiary compliance for eligibility)
- Randomize subject in IWRS if eligibility confirmed
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Dispense study drug; subjects will take loading dose of 3 tablets while on site
- Review eDiary for compliance, re-train subject as needed
- Assess and record any post-dose AEs and SAEs
- Confirm next scheduled visit

6.5.5 Week 1 Telephone Contact Visit

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

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

6.5.6 Week 2 Visit

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

- 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
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Draw blood for clinical laboratory tests
  - Hematology
  - Chemistry
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Collect returned study drug

- Utilize IWRS to assign new bottle of study drug
- Confirm next scheduled visit date

6.5.7 Week 4 Visit

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

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign new bottle of study drug
- Review eDiary for compliance, re-train subject as needed
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.8 Week 6 Visit

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

- 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
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain vital signs
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Perform targeted physical examination, including weight
- Assess and record any AEs and SAEs
- Collect returned study drug
- Utilize IWRS to assign new bottle of study drug
- Review eDiary for compliance, re-train subject as needed
- Confirm next scheduled visit

6.5.9 Week 10 Visit

The Week 10 visit occurs 70 days (± 7 days) after the Baseline visit. At the Week 10 visit, the following procedures and assessments are to be performed:

- Ask the subject to complete the DLQI, HADS, and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain ECG
- Obtain vital signs
- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)

- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
- Collect PK blood sample
- Assess and record any AEs and SAEs
- Collect returned study drug
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Review eDiary for compliance, inform subject to continue entering WI-NRS score until Follow-up visit
- Review study drug compliance with re-training as required
- Confirm next scheduled visit date

6.5.10 Follow-up Visit

The required Follow-up visit occurs 21 or 35 (+7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early. The required follow-up period is defined as a minimum of 3 weeks for those subjects who will enroll in the one-year open-label safety study on the date of the follow-up visit, and as 5 weeks for those subjects who will not be enrolled in the one-year open-label safety study of serlopitant. Should a subject present for the follow-up visit prior to 5 weeks after the last dose of study drug and be excluded from participation in the one-year study for any reason, the subject will be required to return at 5 weeks after the last dose of study drug for a complete follow-up visit.

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

- Register visit into the IWRS
- Ask the subject to complete the HADS and ESS questionnaires
- Assess and record any changes in the subject's concomitant medications
- Female subjects should be queried for presence of new breast masses or abnormal discharge, and abnormal vaginal bleeding or discharge
- Review menstrual diary and record dates of menstrual flow (if applicable)
- Obtain vital signs

- Perform targeted physical examination, including weight
- Perform IGA PN-A
- Perform IGA PN-S
- Obtain ECG
- Obtain photos (at selected sites, only subjects that signed photography consent)
- Perform a urine pregnancy test for females of childbearing potential (with positive or equivocal results confirmed by a serum pregnancy test)
- Draw blood for clinical laboratory tests (morning blood sampling due to Endocrine assessments)
  - Reproductive endocrine labs for females under 55 years of age at consent
  - Endocrine
  - Hematology
  - Chemistry
- Assess and record any AEs and SAEs
- Collect eDiary device, review eDiary for compliance

6.5.11 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) –GCP guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If provided, the reason (adverse event, study burden, lack of efficacy, other) a subject withdrew consent will be recorded in the electronic Case Report Form (eCRF). The PI or site staff must make every effort to contact subjects who are suspected of being lost to follow-up. Attempts to contact such subjects must be documented in the subject's source documents.

7 ASSESSMENT OF SAFETY

7.1 Definitions

7.1.1 Adverse Event

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

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

7.1.2 Serious Adverse Event

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

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

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

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

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

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

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

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

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

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

7.1.4 Deaths

Any deaths that occur from the time of informed consent to the follow-up visit, regardless of attribution, must be reported within 24 hours of investigator's awareness of the death. See Safety Form Completion Instructions for complete instructions.

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

7.1.5 Pregnancies and Contraception Requirements for Females

For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal, unless permanently surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female.

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

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

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

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

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

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

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

7.1.6 Worsening of Pruritus or PN

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

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

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

All AEs entered into the eCRF will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 study drug treatment or participation in the study is not the cause of the AE or SAE.

7.4 Reporting Serious Adverse Events to the Sponsor and Institutional Review Board or Ethics Committee

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

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

Please see the Safety Form Report Completion Instructions for safety reporting instructions.

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

7.5 Reporting Serious Adverse Events to Regulatory Authorities and Study Investigators

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

7.6 Emergency Unblinding

Emergency unblinding is available 24 hours per day/7 days per week and will be performed via IVRS. An investigator may unblind a subject's treatment assignment only when knowledge of the investigational product is essential for the welfare of a subject. There is no specific antidote for serlopitant and usual supportive medical management is recommended in the case of a medical emergency.

8 STATISTICAL METHODS

All statistical processing will be performed using SAS® unless otherwise stated. One interim analysis may be performed. Endpoints will be summarized with descriptive statistics by treatment group and visit. For continuous variables, the following information will be presented: n (number of subjects), mean, standard deviation, median, minimum and maximum. For categorical variables counts and percentages will be used. Summary statistics for imputed efficacy data will be reported based upon imputed data.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Subjects who withdrew from the study due to a lack of efficacy, or used an excluded therapy to treat worsening of pruritus or PN, will be defined as non-responder.

As one sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). As a second sensitivity analysis, a repeated measures model will be used on observed data. Additionally, a tipping point analysis will be done as a sensitivity analysis for the primary endpoint.

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

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

8.1 Decision Rule and Sample Size

This study will use a 5% two-sided alpha level. While the alpha level is two-sided, clinically relevant results require a serlopitant benefit. Statistical significance for the key secondary efficacy endpoints requires statistical significance for the primary efficacy endpoint (i.e. stepdown testing from primary to key secondary endpoints). The key secondary efficacy endpoints will be tested in order starting with the Week 4 WI-NRS 4-point responder rate, and then the Week 2 WI-NRS 4-point responder rate.

The target sample size of 280 randomized and dosed subjects (140 per group) has been determined based upon a 1:1 allocation of subjects to treatment groups and a 5% alpha level. Completed Phase 2 studies indicate that placebo responder rates vary between CCI% and CCI% and serlopitant rates between CCI% and CCI%. A sample size of 280 subjects provides >90% power assuming a placebo responder rate of CCI% and a serlopitant rate of CCI%.

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

8.2 Handling of Missing Data

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

The primary method of handling missing efficacy data will be MCMC multiple imputation. Subjects who withdrew from the study due to a lack of efficacy, or used an excluded therapy to treat worsening of pruritus or PN, will be defined as non-responder. Imputation will be conducted within each treatment group independently, so the pattern of missing observations in one treatment group cannot influence missing value estimations in another. For each imputation process, 25 imputations will be performed.

If a subject fails to complete their eDiary for the week prior to Week 10, the primary endpoint (WI-NRS) data will be missing, unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. If the Week 10 value is missing for any other reason, the change from baseline value will be based on imputed data. Missing Week 10 WI-NRS values from which the 4-point responder status is derived will be estimated by MCMC.

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

1. Using the daily eDiary data, calculate Baseline and Week 2 through Week 10 values by averaging available values. In order to compute a week's average, a minimum of 4 values must be available for that week. The weekly average will be imputed when there are fewer than 4 values available.

2. From step 1, create a dataset for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing WI-NRS values in each dataset will be filled in using the MCMC method to generate 25 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset.

Syntax:

```
proc mi data=datain out=dataout seed=&seed. Nimpute=25 <options>;
  where trtpn=(TRT);   /* Note TRT = [1, 2]; depending on treatment group */;
  mcmc chain=single;
  var baseline week1 week2 week3 week4 week5 week6 week7 week8 week9
week10;
run;
```

3. From each complete dataset, the dichotomous responder rate will be determined. Each complete dataset will be analyzed as specified for the particular analysis.

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

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

CCI

8.3 Analysis Populations

The primary efficacy population will be the Intent-to-Treat (ITT) and will include all randomized subjects who were dispensed study drug. Subjects will be analyzed within the treatment group to which they are randomized.

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

The Per Protocol (PP) population will include all subjects in the safety population who complete the Week 10 evaluations without any significant protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). Analyses performed on the Per Protocol population will be considered supportive. The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Receives a strong CYP3A4 inhibitor (See Appendix B);
- Receives an excluded medication for treatment of pruritus or PN;
- Have not been compliant with the dosing regimen (i.e. subjects must comply with 80–120% of the expected dosage of study medication during participation in the study);
- Out of visit window at the Week 10 visit by ±7 days

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

8.4 Subject Disposition

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

8.5 Subject Characteristics

Demographic and other baseline characteristics will be summarized.

8.6 Prior and Concomitant Medications

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

Prior therapies (including over-the-counter medications) used to treat the signs and symptoms of PN within the prior 2 years will be reported. Prior medications will be summarized by ATC level and preferred drug name and listed.

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

8.7 Treatment Compliance and Extent of Exposure

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

8.8 Efficacy Analyses

All efficacy endpoints will be summarized within the ITT and PP populations using descriptive statistics by time point and treatment. Results including averaged imputed values will be summarized at Baseline, Week 2 (if available), 4, 10 and Follow-up, and the change from baseline for these measures will be summarized at Week 2, 4, 10 and Follow-up. The WI-NRS and change from baseline will also be presented for each study day.

8.8.1 Primary Efficacy

The difference in the primary efficacy outcome measure (WI-NRS 4-point responder rate at Week 10) will be tested using a CMH test controlling for the 'as randomized' stratification factors. Conceptually the hypotheses being tested are:

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

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

8.8.2 Key Secondary Efficacy

The differences between treatment groups for the key secondary efficacy endpoints, Week 2 WI-NRS 4-point responder rate and Week 4 WI-NRS 4-point responder rate, will be the CMH test identical to the one used for the primary endpoint.

The preceding tests are to be conducted for the ITT population and the PP populations.

8.8.3 Additional Secondary Efficacy

Additional secondary efficacy endpoints which may be drawn from the primary and key secondary imputations (including all WI-NRS endpoints) will be analyzed using the imputed data. Additional secondary efficacy endpoints otherwise will be analyzed using available data. P-values will be included for descriptive purposes only.

Additional secondary efficacy endpoints which are dichotomous (responder) will include analyses analogous to the primary and key secondary efficacy analyses.

Additional secondary efficacy endpoints based on change from baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and stratification factor as fixed effects and the baseline value as a covariate. Both least squares means and observed means will be presented.

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

8.9 Sensitivity Analyses

8.9.1 Last Observation Carried Forward

In the first set of sensitivity analysis, missing values will be imputed using LOCF. Data will be imputed using LOCF unless the subject withdrew from the study due to a lack of efficacy, or the subject used an excluded therapy to treat worsening of pruritus or PN, in which case their responder status will be defined as non-responder. Each primary and key secondary endpoint will be analyzed as it was using the multiply imputed data.

8.9.2 Repeated Measures Analysis

The second set of sensitivity analyses will be performed on observed data.

The dichotomized primary and key secondary WI-NRS endpoints will be analyzed with a repeated measures logistic regression model (generalized estimating equations), with the

dichotomized endpoint as the dependent variable and treatment, stratification factor and visit (Weeks 2, 4, 10) as independent factors

Change from baseline in DLQI to Week 10 will be analyzed with a repeated measures ANCOVA, with treatment, stratification factor and applicable timepoints as independent factors and a covariate of baseline value.

8.9.3 Tipping Point Analysis

A sensitivity analysis for the handling of missing data for the primary efficacy endpoint will be carried out using a tipping point analysis.

8.10 Safety Analyses

8.10.1 Adverse Events

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

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

8.10.2 Clinical Safety Laboratory Results

Clinical safety laboratory values will be measured by a central laboratory. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit.

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

8.10.3 Vital Signs

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

8.10.4 Electrocardiograms

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

8.10.5 Physical Exams

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

8.10.6 Menstrual Diaries

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

8.10.7 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.

8.10.8 Epworth Sleepiness Scale

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

8.11 Interim Analyses

No interim analysis is planned.

8.12 Population Pharmacokinetics Analysis

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

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 guideline. The protocol, ICF, other written subject information, and any proposed study advertising material must be submitted to the IRB or EC for written approval. IRB or EC approval of these documents will be provided to the

investigator. The study will not start until the IRB or EC has granted its approval of the study materials and procedures.

Protocol amendments will be submitted to the IRB or EC as explained in Section 9.1. SAE information will be submitted to the IRB or EC as explained in Section 7.4.

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

9.7 Disclosure and Confidentiality

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

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

9.8 Records and Electronic Case Report Forms

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

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

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

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

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

9.9 Good Clinical Practices and Ethical Study Conduct

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

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

9.10 End of Study Notification

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

9.11 Publication of Results

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

9.12 Final Report

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

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APPENDIX A SCHEDULE OF ACTIVITIES AND ASSESSMENTS

Table 2 Schedule of Visit Activities

Examination	Screening	Mid-Screening[TC]	Baseline[1]	Week 1[TC] (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 10 (± 7 days)	F/U[2]	Early Treatment Discontinuation
Demographics	X									
Informed consent	X									
WI-NRS[3]	X	X	X	X	X	X	X	X		
DLQI			X			X		X		X
HADS, ESS			X			X		X	X	X
ECG	X				X	X		X	X	X
Vital signs	X		X		X	X	X	X	X	X
Medical history (and prior medications)	X	X	X							
Physical exam[4]	X		X		X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X
Labs[5]	X				X			X	X	X
Urine pregnancy test[6]	X		X			X	X	X	X	X
PK blood draw					X	X		X		
Review of I/E criteria	X	X	X							
IGA PN-A and IGA PN-S			X		X	X		X	X	X
Photography (selected sites)			X					X	X	X
Dispense/review menstrual diary (if applicable)	X		X		X	X	X	X	X	X
Dispense/collect eDiary	X								X	X
eDiary review/compliance[7]		X	X	X	X	X	X	X	X	
Dispense and/or collect study drug			X		X	X	X	X		X
Review study drug compliance					X	X	X	X		
AEs/SAEs[8]	X	X	X	X	X	X	X	X	X	X

[TC]Telephone Contact: The Mid-Screening telephone contact should only occur for subjects who require a washout longer than 2 weeks, at least 15 days prior to the scheduled Baseline visit.

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

[2]The Follow-up (F/U) visit occurs 21-35 days (+ 7 days) after the Week 10 visit or the last dose of study drug for subjects who discontinue study drug early.

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

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

[5]Labs are ideally performed in the morning, particularly at visits with endocrine assessments (including Reproductive Endocrinology for females under 55 at age of consent) at Screening, Week 10 and Follow Up. Iron Studies, serum IgE and Serology labs are done only at Screening visit; endomysial antibody test and other optional studies only performed at Screening;

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

[7]See Table 3 for eDiary assessments

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

Table 3 Schedule of eDiary Assessments

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

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

APPENDIX B LIST OF STRONG CYP3A4 INHIBITORS

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

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

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

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

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

APPENDIX C WORST ITCH NUMERIC RATING SCALE QUESTIONNAIRE

NRS for Itch Intensity

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

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

Score	Category	Description: Activity (IGA PN-A)
0	**Clear**	No nodules have excoriations or crusts
1	**Almost Clear**	Very small proportion of nodules have excoriations or crusts (up to approximately 10% of all nodules)
2	**Mild**	Minority of nodules have excoriations or crusts (approximately 11- 25% of all nodules)
3	**Moderate**	Many nodules have excoriations or crusts (approximately 26- 75% of all nodules)
4	**Severe**	Majority of nodules have excoriations or crusts (approximately 76-100% of all nodules)

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

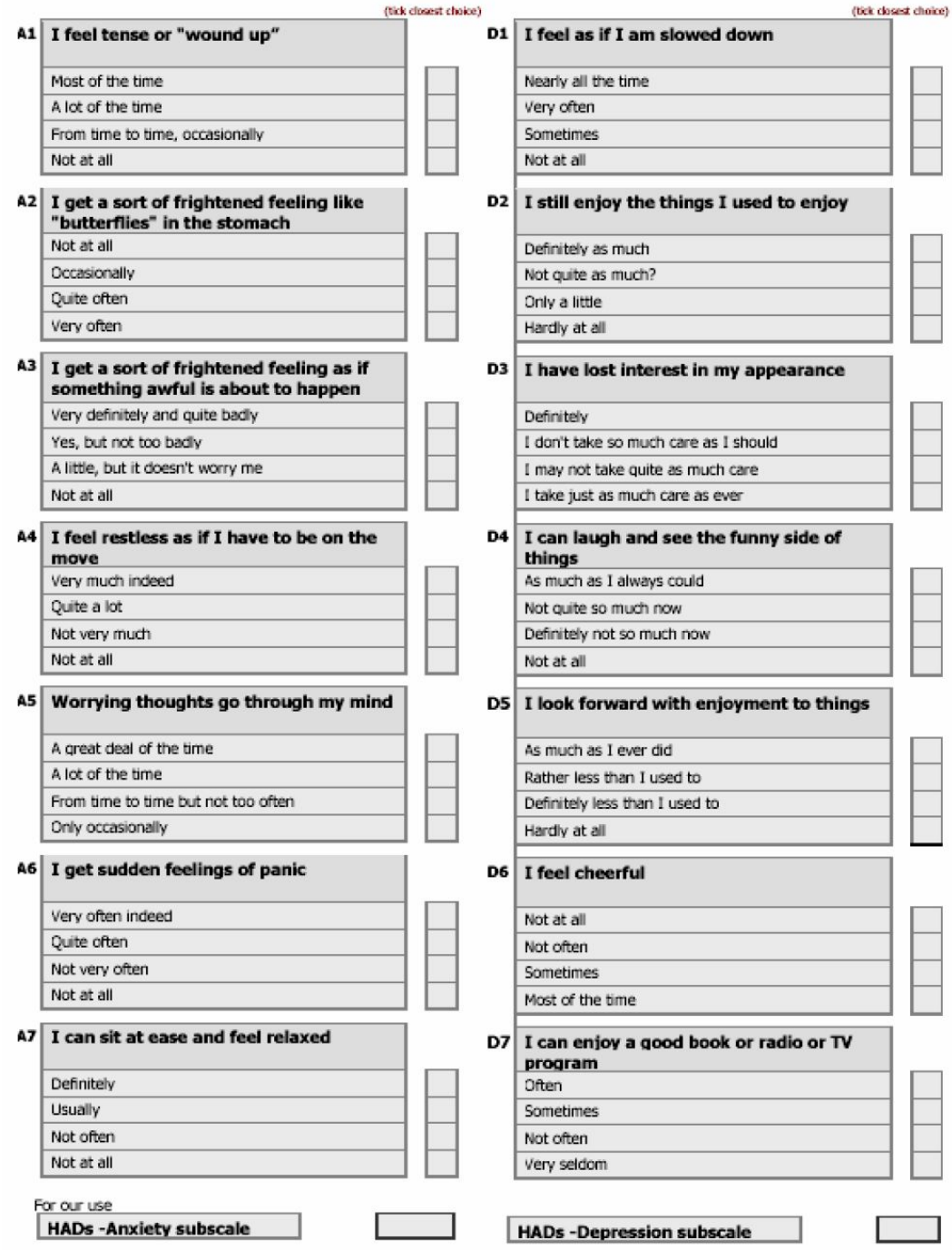
Score:

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