CLINICAL STUDY PROTOCOL

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF SERLOPITANT FOR THE TREATMENT OF REFRACTORY CHRONIC COUGH
IND No.:	135540
ClinicalTrials.gov ID:	TBD
EudraCT Number:	2017-003250-16
Protocol No.:	MTI-110
Protocol Version / Date:	Version 2.0 / 28-AUG-2017
Development Phase:	Phase 2
Sponsor:	Menlo Therapeutics Inc. 4085 Campbell Avenue, Suite 200 Menlo Park, CA 94025 USA

Confidentiality Statement:

SIGNATURE PAGE FOR INVESTIGATOR(S)

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

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Approved by:

[redacted]	[redacted]	28 Aug 2017
Chief Medical Officer	Signature	Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Refractory Chronic Cough
Protocol Number:	MTI-110
Sponsor:	Menlo Therapeutics Inc.
Study Centers:	Approximately 45 sites in the USA and UK
Development Phase:	Phase 2
Study Objectives:	The primary objective of this study is to assess the effectiveness of serlopitant for the treatment of refractory chronic cough after 12 weeks of treatment in reducing 24-hour objective cough frequency. The secondary objectives are as follows: • To evaluate the effectiveness of serlopitant as compared to placebo after 4 and 8 weeks of treatment in reducing 24-hour objective cough frequency • To evaluate the effectiveness of serlopitant as compared to placebo after 4, 8 and 12 weeks of treatment in reducing awake objective cough frequency • To evaluate the effectiveness of serlopitant as compared to placebo after 4, 8 and 12 weeks of treatment in reducing sleep objective cough frequency • To evaluate the effectiveness of serlopitant in: ◦ Reducing the cough severity measured by a Visual Analog Scale (VAS) ◦ Improving cough-specific quality of life (LCQ) • To assess the safety and tolerability of repeated oral doses of serlopitant in subjects with treatment refractory chronic cough
Study Design:	This is a 12-week randomized, parallel-group, double-blind, placebo-controlled study of serlopitant in subjects with treatment refractory chronic cough. Approximately 170 subjects who meet entry criteria will be randomly assigned to serlopitant 5 mg or matching placebo in a 1:1 ratio for up to 84 days. The randomization will be stratified by country and gender. The study will consist of three periods, for a total study period of approximately 18 weeks: • Screening period: 14 days • Treatment period: 84 days • Follow-up period: 28 days During the screening period, subjects will undergo eligibility evaluations. Subjects must be willing to comply with restrictions on allowable concomitant therapies for the duration of the study. At the Baseline visit, eligible subjects will be randomly assigned to one of two treatment groups and will have baseline cough monitoring conducted. One day after the Baseline visit, subjects will take a loading dose (3 tablets taken orally) in the morning 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 in the morning. Subjects will be instructed to take all doses at approximately the same time each day and no sooner than 2 hours before or after a meal. The primary efficacy endpoint will be assessed at Day 84 of treatment. After completion of the 84-day treatment period, all subjects will enter a 28-day follow-up period. Subjects who discontinue treatment early at any time during the treatment period will have an Early Treatment Discontinuation (ETD) visit within 7 days after their last dose of study drug in addition to a follow-up visit.
Planned Sample Size:	Approximately 170 subjects will be randomized.
Study Population:	The study will consist of adults with a history of treatment refractory chronic cough. Inclusion Criteria: Subjects who meet all of the following criteria will be included in the study: 1. Female and males between 18 and 80 years of age inclusive, at Screening 2. Chest radiograph or computed tomography (CT) Thorax within the last 5 years not demonstrating any abnormality considered to be significantly contributing to the chronic cough in the opinion of the Principal Investigator and Menlo Therapeutics Medical Monitor 3. Have a diagnosis of treatment refractory chronic cough or unexplained cough for at least one year (see American College of Chest Physicians/British Thoracic Society (ACCP/BTS) guidelines in Appendix C) 4. At Screening have a score of ≥ 40mm on the Cough Severity VAS 5. At Baseline (Day 0) have a score of ≥ 40mm on the Cough Severity VAS 6. All female subjects who are of childbearing potential must practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the initial screening visit until 4 weeks after last dose of study drug. Please refer to Section 7.1.5 for acceptable methods of contraception 7. Have provided written informed consent 8. Are willing and able to comply with all aspects of the protocol Exclusion Criteria: 1. Prior treatment with serlopitant or other neurokinin-1 receptor (NK_1-R) antagonists (e.g., aprepitant, orvepitant) 2. Current smoker or individuals who have given up smoking within the past 12 months 3. FEV1/FVC < 60% 4. Body mass index (BMI) <18 kg/m^2 or ≥ 40 kg/m2 at Screening 5. History of upper or lower respiratory tract infection or recent significant change in pulmonary status within 4 weeks of the Baseline Visit (Day 0) 6. History of cystic fibrosis 7. History of opioid use within 1 week of the Baseline Visit (Day 0)

	8. Requiring concomitant therapy with prohibited medications (see Section 5.7) 9. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to the Baseline Visit (Day 0), whichever is longer 10. Treatment with strong CYP3A4 inhibitors within 4 weeks prior to the Baseline Visit (Day 0) (see Appendix B) 11. Treatment with any investigational therapy within 4 weeks (investigational biologic therapies within 8 weeks) prior to the Baseline Visit (Day 0) 12. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x the upper limit of normal (ULN) during screening 13. Positive test for any drug of abuse 14. History of malignancy within 5 years prior to the Baseline Visit (Day 0), with the exception of completely treated and non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin 15. Any known psychiatric diagnosis meeting DSM-5 criteria 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. Examples of such DSM-5 diagnoses include but are not limited to major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder. 16. Known active hepatitis infection 17. Known history of human immunodeficiency virus (HIV) infection 18. History of hypersensitivity to serlopitant or any of its components 19. Currently pregnant or breastfeeding female subject 20. Females of childbearing potential who are unable or unwilling to practice highly effective contraception (pregnancy prevention) 21. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject, including clinically significant ECG abnormalities during screening 22. 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 84 days, following a 3-tablet loading dose on the first day of the treatment period. Matching placebo: Once daily by mouth for 84 days, following a 3-tablet loading dose on the first day of the treatment period.

Prohibited Concomitant Therapy	The following therapies are excluded from 1 week prior to the Baseline Visit (Day 0) through the follow-up period: • Opioids (including codeine). Opioids (including codeine), if required for other indications, are permitted provided that subjects are receiving a stable dose for at least one week prior to the Baseline Visit (Day 0) and still experiencing a troublesome cough. Subjects must remain on a stable dose for the duration of the treatment period. The following cough therapies are excluded from 2 weeks prior to the Baseline Visit (Day 0) through the end of the treatment period: • Dextromethorphan • Guaifenesin • Chlorpheniramine maleate extended release tablets • Benzonatate The following therapies are excluded from 2 weeks prior to the Baseline Visit (Day 0) through the follow-up period: • Pregabalin, gabapentin, thalidomide, or amitriptyline for the treatment of cough. Pregabalin, gabapentin, thalidomide, or amitriptyline if required for other indications, is permitted if subjects are receiving a stable dose and still experiencing a troublesome cough. Subjects must remain on a stable dose for the duration of the treatment period. The following therapies are excluded from 4 weeks prior to the Baseline Visit (Day 0) through the follow-up period: • Systemic immunosuppressive/immunomodulatory therapies (including but not limited to PDE4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, or phototherapy) • Strong CYP3A4 inhibitors (See Appendix B) • Any investigational therapy The following therapies are excluded from 8 weeks prior to the Baseline Visit (Day 0) through the follow-up period: • Biologic therapies • Investigational biologic therapies The following therapy is excluded from 12 weeks prior to the Baseline Visit (Day 0) through the follow-up period: • Treatment with an ACE-inhibitor

Primary Efficacy Endpoint:	The primary efficacy endpoint is: Change from Baseline in 24-hour objective cough frequency after 12 weeks (Day 84) of treatment.
Secondary Efficacy Endpoints:	<u>Key Secondary</u> • Change from Baseline in awake objective cough frequency after 12 weeks (Day 84) of treatment • Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour at Week 12 (Day 84) • Proportion of subjects with ≥30% reduction in awake objective cough frequency per hour at Week 12 (Day 84) • Change from Baseline in Cough Severity Visual Analog Scale (VAS) at Week 12 (Day 84) <u>Other Secondary</u> • Change from Baseline in 24-hour objective cough frequency after 4 and 8 weeks (Days 28 and 56) of treatment • Change from Baseline in awake objective cough frequency after 4 and 8 weeks (Days 28 and 56) of treatment • Change from Baseline in 24-hour objective cough frequency at the Follow-Up visit (Day 112) • Change from Baseline in sleep objective cough frequency after 4, 8 and 12 weeks (Days 28, 56 and 84) of treatment • Change from Baseline in Cough Severity Visual Analog Scale (VAS) at Weeks 4 and 8 (Days 28 and 56) • Change from Baseline in Leicester Cough Questionnaire (LCQ) individual Domain and Total scores • Patient's Global Impression of Change (PGIC) • Clinician's Global Impression of Change (CGIC)
Safety Endpoints:	<u>Safety Assessments</u> Safety will be assessed through monitoring of adverse events (AEs), physical examinations (including vital signs), electrocardiograms (ECGs), and laboratory tests. Safety assessment frequency is shown in the Schedule of Assessments and Procedures. Safety endpoints include the following: • Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Change in clinical laboratory parameters following study drug exposure • Changes in vital sign and ECG parameters following study drug exposure • Plasma concentrations of serlopitant and metabolites

Decision Rule and Sample Size	A total of 170 subjects (85/arm) in 1:1 ratio of serlopitant 5 mg or placebo will provide 90% power to detect a 25% relative reduction (placebo-adjusted ratio of 0.75) in 24-hour objective cough frequency or awake objective cough frequency using a two-sample t-test at a one-sided significance level of 0.05. This assumes that 24-hour cough frequency or awake cough frequency follows a log-normal distribution with a CV of 0.64. This sample size also considers an expected dropout rate of 15%. The comparisons related to the primary and key secondary objectives will be done in a hierarchical manner to control the familywise error rate. The testing procedure will start by testing the primary endpoint and then proceed to the key secondary endpoints by following the order as specified in Section 8.9.4.
Analysis Sets:	Efficacy Analysis Sets Full Analysis Set (FAS) – All randomized subjects who have taken at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period. Participants will be analyzed according to the treatment group to which they are randomized. Safety Analysis Sets The safety analysis set will consist of all subjects randomized who receive at least one dose of study medication. Subjects will be classified based upon the treatment received. PK Analysis Set The PK analysis set will consist of all subjects who receive ≥ 1 dose of serlopitant and who have at least 1 post-dose PK blood sample available for analysis.
Statistical Methods:	Efficacy Analyses: The FAS population will serve as the primary population for the analysis of efficacy data in this study. The primary efficacy endpoint of this study is change from Baseline in 24-hour objective cough frequency after 12 weeks (84 days) of treatment. As the change in 24-hour cough frequency may have a skewed and wide distribution, the primary analysis for the primary endpoint will be analyzed on the natural log scale. The difference between serlopitant (5 mg) and placebo will be estimated using a mixed effect repeated measures (MMRM) model. The model will include factors for treatment, visit, country, sex, the interaction of treatment by visit; and the log-transformed baseline value as a covariate. The MMRM model will use all available 24-hour cough frequency data on Day 28, 56, and 84. The geometric mean of the 24-hour coughs per hour will be presented by treatment and by visit. The percent difference change between serlopitant and placebo will be estimated by $100*(e^{diff} - 1)$, where diff is the difference provided by the analysis of the log transformed variable. In order to evaluate the robustness of efficacy results and assess the effect of missing data, additional sensitivity analyses for the primary efficacy variables will be employed. Safety Analyses: 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. 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 observed vital signs and ECG data and change from Baseline for each measurement day will be summarized with descriptive statistics.
Expected Duration of Subject's Participation	Approximately 126 days: 14 days of screening, 84 days of treatment, and a follow-up period of 28 days.

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

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACCP	American College of Chest Physicians
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Mullerian Hormone
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BTS	British Thoracic Society
CGIC	Clinician's Global Impression of Change
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomograghy
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ETD	Early treatment discontinuation
FAS	Full Analysis Set
iDMC	Independent Data Monitoring Committee
DSM	Diagnostic Statistical Manual
ICF	Informed Consent Form
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LCQ	Leicester Cough Questionnaire
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK_1-R	Neurokinin-1 receptor
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
QoL	Quality of life
RO	Receptor Occupancy
SAE	Serious adverse event
SOC	System organ class
SP	Substance P
TEAE	Treatment-emergent adverse event
UK	United Kingdom
USA	United States of America
VAS	Visual Analog Scale

1 INTRODUCTION

1.1 Refractory Chronic Cough

Cough is a common symptom frequently associated with other conditions such as an upper respiratory infection, chronic obstructive pulmonary disease (COPD), or asthma. In cough guidelines, such as those published by the American College of Chest Physicians, cough is characterized by the length of time a patient is coughing: Acute - up to 3 weeks, Sub Acute - from 3 to 8 weeks, and Chronic - greater than 8 weeks (Irwin 2006). Patients who present to a physician for a persistent cough are evaluated and treated for obvious and common causes of cough. If a patient continues to cough, he/she is evaluated for conditions that are commonly associated with chronic cough. These are asthma, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS) (Dicpinigaitis 2011). According to the cough guidelines, a patient may be evaluated for less common diseases based on the patient's history, other symptoms, or physical findings. Patients in whom no treatable cause of their cough can be found are characterized as having "refractory chronic cough" (Gibson 2016).

Patients with refractory chronic cough may represent up to 12% of the general population. Patients are most commonly women (approximately 2/3-3/4 of patients are women) of approximately 45 to 75 years of age. Patients most commonly cough while awake for approximately 20 times per hour to as much as several hundred times per hour (Abdulqawi 2014). The cough may last for many years with some patients reporting having coughed for a median of 12 years in a recent study (Abdulqawi 2014). Patients with refractory chronic cough report that their condition is frequently disabling and has a marked effect on their quality of life as measured by instruments such as the Leicester Cough Questionnaire (LCQ) (Birring 2003, Kelsall 2008).

Treatment options for refractory chronic cough are very limited. There are no approved drug treatments for this disease. Patients and clinicians frequently try over-the-counter agents such as dextromethorphan, guaifenesin, and antihistamines with little benefit. Prescription options in the U.S. include codeine and related opiate products and benzonatate, and in the U.K. low-dose oral morphine. Studies have evaluated amitriptyline (Dicpinigaitis 2014) and gabapentin with some patients having some benefit but with some important adverse events (Ryan 2012). Importantly, there have been no FDA approvals for a novel pharmaceutical agent to treat cough in over 50 years.

1.2 Substance P and the Neurokinin-1 Receptor in Cough

As the study of cough and the search for agents that can control the coughing in patients with refractory chronic cough advance, there has been a greater appreciation for the role of the abnormalities in the neuronal pathways that control cough. These pathways include peripheral sensory C and Aδ fibers that are contained in vagal afferent nerves (LaVinka 2013, Mazzone 2007). These nerves have their ganglia in the jugular and nodose ganglion and project their terminals into the nucleus tractus solitarius of the brainstem. It has been proposed by Canning et al that while there are multiple stimuli in the periphery that are involved with the cough reflex, in the central nervous system there are few mediators of the cough (Canning 2009). One of these is through substance P/neurokinin pathway. Neurokinin

A1 antagonists have been found to inhibit cough in several animal models of cough (Canning 2009, Grobman 2016, Mazzone 2005). Therefore, it is proposed that NK_1-R antagonism may play a key role in controlling cough. There have been two recently reported studies with an NK_1-R antagonist in controlling cough. Aprepitant, which is commercially available as an antiemetic, was successful in reducing cough in patients with lung cancer (Harle 2015). Similarly, a study of orvepitant in subjects with refractory chronic cough also showed benefit after one month of treatment (Smith 2017).

1.3 Serlopitant

1.3.1 Serlopitant Background

Serlopitant is a small molecule, highly selective NK1-R antagonist that is administered orally and metabolized by CYP3A4, with a plasma half-life of 45–86 hours. It binds with high affinity to the human NK1-R with a dissociation constant (Kd) of 46 pM; displacing SP binding with a half-maximal inhibition concentration (IC_{50}) of 61 pM. Serlopitant is a potent functional antagonist of SP-induced inositol phosphate generation.

Serlopitant has been extensively studied in animal toxicology studies, including chronic toxicology and carcinogenicity studies. In non-clinical chronic toxicology studies in rats, mice and dogs, treatment related findings of potential clinical significance included increased salivation, decreased body weight gain and food consumption, slight changes in hematology and serum biochemistry parameters, mild increases in liver weight and mild histomorphologic changes. The histomorphologic changes were seen only in rats (not in dogs or mice) and included: very slight ovarian interstitial cell hypertrophy, mammary gland and uterine atrophy; decreased corpora lutea; increased histiocytes in lung and mesenteric lymph nodes; slight skeletal and cardiac muscle degeneration; slight increased hematopoiesis in bone marrow; and slight to moderate vacuolation in kidney tubules. These nonclinical findings occurred at systemic exposures exceeding those anticipated to provide efficacy of serlopitant for pruritus indications in humans (1 to 5 mg tablet daily). No cardiac lesions have been observed in dog toxicity studies up to 9 months in duration nor in a 3-month mouse range-finding study and 2-year mouse carcinogenicity study at exposure higher than the lowest level which caused cardiotoxicity in rats. The no observed adverse effect level (NOAEL) in rats for histomorphological changes in the reproductive tract, mammary gland and bone marrow provides a 2.5-fold margin for the maximum-targeted exposure (5 mg tablet daily). The rat NOAEL for histomorphological changes in muscle and kidney provides a 5-fold margin for the maximum-targeted exposure (5 mg tablet daily).

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

1.3.2 Serlopitant Clinical Data in Phase 1 and Non-Pruritus Studies

In humans, serlopitant has been administered to over 1000 individuals. Single doses up to 400 mg have been well tolerated in healthy young males. Multiple doses of up to 50 mg a

day for 4 weeks have been well tolerated in healthy young males, and a single (loading) dose of 15 mg followed by daily doses of 5 mg for 2 weeks have been well tolerated in elderly males and females. Forty-one (41) subjects received 4 mg liquid filled capsule (LFC) daily (exposure comparable to 5 mg tablets) for 1 year. Plasma concentrations of serlopitant appear to increase in a dose-proportional fashion in both young males and elderly subjects (males and females). Peak plasma concentrations after a single oral dose occurred at ~2 to 4 hours in both young and elderly subjects.

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

1.3.3 Serlopitant in Pruritus-Related Studies

Serlopitant has been evaluated in two completed Phase 2 studies of subjects with chronic pruritus (TCP-101 and TCP-102). In TCP-101, a Phase 2 study of 256 adult subjects 18 to 65 years of age with chronic pruritus), treatment-emergent AEs (TEAEs) were reported for 25.4% of subjects in the placebo group and 32.8%, 36.9%, and 37.5% of subjects in the serlopitant 0.25, 1, and 5 mg groups, respectively. Overall, headache was the most commonly reported TEAE, reported for 6.3% of subjects in the placebo group and 1.6%, 4.6%, and 1.6% of subjects in the serlopitant 0.25, 1, and 5 mg groups, respectively. Somnolence and diarrhea were the TEAEs with the highest overall incidence in the serlopitant groups. Most TEAEs were mild or moderate in severity. Six subjects discontinued study drug due to a TEAE; the events considered treatment-related in the serlopitant groups were diarrhea and gastrointestinal (GI) pain. There was no evidence of meaningful trends in laboratory abnormalities or changes in vital signs.

In TCP-102, a Phase 2 study of 127 adult subjects 18 to 80 years of age with PN, TEAEs were reported for 61.9% of subjects in the placebo group and 71.9% of subjects in the serlopitant 5 mg group. The most common 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). Most TEAEs were mild or moderate in severity. Five subjects (3 serlopitant, 2 placebo) had serious adverse events (SAEs); those considered possibly related to study drug in the serlopitant group were depression, dizziness, and vertigo. Nine subjects discontinued study drug due to a TEAE; those considered treatment-related in the serlopitant groups were pruritus, neurodermatitis, headache, dizziness, and vertigo. No clinically relevant changes were observed in chemistry, hematology, vital signs, or electrocardiogram (ECG) results.

Additional studies are currently ongoing in pruritus associated with atopic dermatitis and epidermolysis bullosa.

1.3.4 Serlopitant in Chronic Cough

Other NK_1-R antagonists (aprepitant and orvepitant) have reported success in pilot studies in treating chronic cough. A study in subjects with lung cancer and cough showed a favorable benefit of treatment with aprepitant (Harle 2015). Similarly, a study of orvepitant in subjects with refractory cough also showed benefit after 1 month of treatment (Smith 2017). Therefore, it is reasonable to study serlopitant in this indication. Serlopitant has several advantages over the other NK_1-R antagonists especially considering its long half-life and favorable safety profile. This study will explore the effectiveness of serlopitant in subjects with refractory chronic cough.

2 STUDY OBJECTIVES

The primary objective of this study is to assess the effectiveness of serlopitant for the treatment of refractory chronic cough after 12 weeks of treatment in reducing 24-hour objective cough frequency.

The secondary objectives are as follows:

- To evaluate the effectiveness of serlopitant as compared to placebo after 4 and 8 weeks of treatment in reducing 24-hour objective cough frequency
- To evaluate the effectiveness of serlopitant as compared to placebo after 4, 8 and 12 weeks of treatment in reducing awake objective cough frequency
- To evaluate the effectiveness of serlopitant as compared to placebo after 4, 8 and 12 weeks of treatment in reducing sleep objective cough frequency
- To evaluate the effectiveness of serlopitant in:
    - Reducing the cough severity measured by a Visual Analog Scale (VAS)
    - Improving cough-specific quality of life (LCQ)
- To assess the safety and tolerability of repeated oral doses of serlopitant in subjects with treatment refractory chronic cough

3 STUDY DESIGN

3.1 Overall Study Design

This is a 12-week randomized, parallel-group, double-blind, placebo-controlled study of serlopitant in subjects with treatment refractory chronic cough.

Approximately 170 subjects who meet entry criteria will be randomly assigned to serlopitant 5 mg or matching placebo in a 1:1 ratio for up to 84 days. The randomization will be stratified by country and gender.

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

- Screening period: 14 days
- Treatment period: 84 days
- Follow-up period: 28 days

Informed consent will occur prior to any protocol-mandated procedures, including the stopping of any excluded therapies. This may occur prior to the initial Screening visit. During the screening period, subjects will undergo eligibility evaluation and will have baseline cough monitoring conducted. Subjects must be willing to comply with restrictions on allowable concomitant therapies for the duration of the study.

At the baseline visit, eligible subjects will be randomly assigned to receive serlopitant 5 mg or placebo. Subjects will take a loading dose (3 tablets taken orally) in the morning 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 in the morning. Subjects will be instructed to take all doses at approximately the same time each day and no sooner than 2 hours before or after a meal.

The primary efficacy endpoint will be assessed at Day 84 of treatment.

After completion of the 84-day treatment period, all subjects will enter a 28-day follow-up period. Subjects who discontinue treatment early at any time during the treatment period will have an Early Treatment Discontinuation (ETD) visit within 7 days after their last dose of study drug in addition to a follow-up visit.

3.2 Rationale for Study Design and Dose Selection

Serlopitant has not been studied in patients with refractory chronic cough. However, serlopitant has been studied extensively in other indications. It is currently being advanced into Phase 3 studies in pruritus.

In the TCP-101 study, serlopitant 5 mg and 1 mg taken daily for 6 weeks were superior to placebo for the reduction of pruritus. Similarly, in the TCP-102 study in patients with prurigo nodularis, serlopitant 5 mg taken daily for 8 weeks was superior to placebo for the reduction of pruritus. In both the TCP-102 and TCP-101 studies, serlopitant was generally well-tolerated and demonstrated an overall favorable safety profile at the doses evaluated.

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

The serlopitant 5 mg dose was selected for this study based on the following factors:

- The favorable efficacy, safety, and tolerability profile of serlopitant at the 5 mg dose level, as demonstrated in the TCP-101 and TCP-102 studies. These data are supported by safety experience across the serlopitant clinical development program. Over 250 subjects have been exposed to serlopitant at doses equivalent to the 5 mg tablet daily for at least 6 weeks, and ~40 subjects have been exposed for up to one year.
- Human CNS PET receptor occupancy (RO) data for serlopitant in healthy young males (Study P002) demonstrated a plasma concentration - RO relationship fitted with a maximum effect (E_{max}) model resulting in an E_{max} of 97%, EC_{50} of 22.9 nM, and EC_{90} of 294 nM. Based on this modeling the steady state trough concentration in adults taking serlopitant 5 mg tablets once-daily is predicted to achieve ~93% RO. In previous dose-ranging experience with the NK_1-R antagonist aprepitant, optimal clinical efficacy for the relief of chemotherapy-induced nausea and vomiting (CINV) was achieved at dose levels resulting in > 90% CNS NK_1 RO.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in 24-hour Cough Frequency after 12 weeks (Day 84) of treatment.

3.3.2 Key Secondary Efficacy Endpoints

- Change from Baseline in awake objective cough frequency after 12 weeks (Day 84) of treatment
- Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour at Week 12 (Day 84)
- Proportion of subjects with ≥ 30% reduction in awake objective cough frequency per hour at Week 12 (Day 84)
- Change from Baseline in Cough Severity Visual Analog Scale (VAS) at Week 12 (Day 84)

3.3.3 Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints include the following:

- Change from Baseline in 24-hour objective cough frequency after 4 and 8 weeks (Days 28 and 56) of treatment

- Change from Baseline in awake objective cough frequency after 4 and 8 weeks (Days 28 and 56) of treatment
- Change from Baseline in 24-hour objective cough frequency at the Follow-Up visit (Day 112)
- Change from Baseline in sleep objective cough frequency after 4, 8 and 12 weeks (Days 28, 56 and 84) of treatment
- Change from Baseline in Cough Severity Visual Analog Scale (VAS) at Weeks 4 and 8 (Days 28 and 56)
- Change from Baseline in Leicester Cough Questionnaire (LCQ) individual Domain and Total scores
- Patient's Global Impression of Change (PGIC)
- Clinician's Global Impression of Change (CGIC)

3.3.4 Safety Endpoints

Safety endpoints include the following:

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

3.4 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 170 adult subjects with a history of treatment refractory chronic cough will be randomized into this study.

4.2 Inclusion Criteria

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

1. Female and males between 18 and 80 years of age inclusive, at Screening
2. Chest radiograph or CT Thorax within the last 5 years not demonstrating any abnormality considered to be significantly contributing to the chronic cough in the opinion of the Principal Investigator and Menlo Therapeutics Medical Monitor
3. Have a diagnosis of treatment refractory chronic cough or unexplained cough for at least one year (see ACCP/BTS guidelines in Appendix C)
4. At Screening have a score of ≥ 40mm on the Cough Severity VAS
5. At Baseline (Day 0) have a score of ≥ 40mm on the Cough Severity VAS
6. All female subjects who are of childbearing potential must practice highly effective contraception (i.e., pregnancy prevention method with a failure rate of < 1% per year) from the time of the initial Screening visit until 4 weeks after last dose of study drug. Please refer to Section 7.1.5 for acceptable methods of contraception
7. Have provided written informed consent
8. Are willing and able to comply with all aspects of the protocol

4.3 Exclusion Criteria

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

1. Prior treatment with serlopitant or other neurokinin-1 receptor (NK1-R) antagonists (e.g., aprepitant, orvepitant)
2. Current smoker or individuals who have given up smoking within the past 12 months
3. FEV1/FVC < 60%
4. Body mass index (BMI) < 18 kg/m2 or ≥ 40 kg/m2 at Screening
5. History of upper or lower respiratory tract infection or recent significant change in pulmonary status within 4 weeks of the Baseline Visit (Day 0)
6. History of cystic fibrosis
7. History of opioid use within 1 week of the Baseline Visit (Day 0)
8. Requiring concomitant therapy with prohibited medications (see Section 5.7)
9. Treatment with biologic therapies within 8 weeks or 5 half-lives prior to the Baseline Visit (Day 0), whichever is longer
10. Treatment with strong CYP3A4 inhibitors within 4 weeks prior to the Baseline Visit (Day 0) (see Appendix B)
11. Treatment with any investigational therapy within 4 weeks (investigational biologic therapies within 8 weeks) prior to the Baseline Visit (Day 0)

12. Serum creatinine, total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x the upper limit of normal (ULN) during screening
13. Positive test for any drug of abuse
14. History of malignancy within 5 years prior to the Baseline Visit (Day 0), with the exception of completely treated and non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin
15. Any known psychiatric diagnosis meeting DSM-5 criteria 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. Examples of such DSM-5 diagnoses include but are not limited to major depressive disorder, bipolar disorder, schizophrenia, psychotic disorder, intellectual disability, severe alcohol use disorder
16. Known active hepatitis infection
17. Known history of human immunodeficiency virus (HIV) infection
18. History of hypersensitivity to serlopitant or any of its components
19. Currently pregnant or breastfeeding female subject
20. Females of childbearing potential who are unable or unwilling to practice highly effective contraception (pregnancy prevention)
21. Presence of any medical condition or disability that, in the investigator's opinion, could interfere with the assessment of safety or efficacy in this trial or compromise the safety of the subject, including clinically significant ECG abnormalities during screening
22. 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).

The tablets will be supplied in bottles, with 18 tablets per bottle. Two bottles will be issued via Interactive Web Response System (IWRS) at Baseline and at the Day 28 and Day 56 visits, for a total of 6 bottles dispensed for subjects completing 84 days 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) in the morning 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 in the morning. Subjects will be instructed to take all doses at approximately the same time each day and no sooner than 2 hours before or after a meal.

5.4 Dose Modification

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

5.5 Missed or Delayed Doses

Each dose of study drug after the first dose must be administered once daily in the morning, no sooner than 2 hours before or after a meal. If the morning dose is missed or delayed by 8 or more hours, that dose should be skipped, and the following dose should be taken in the morning of the following day. The skipped dose will be considered and documented as a missed dose.

5.6 Study Drug Discontinuation

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

- A female subject becomes pregnant
- Subject decision to discontinue study drug treatment, or subject decision to withdraw consent from the study
- The subject receives a strong CYP3A4 inhibitor
- Any medical condition that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion
- Discontinuation is deemed to be in the best interest of the subject, in the investigator's and/or Sponsor's opinion
- The subject experiences a NCI CTCAE Grade 2 or higher treatment emergent AE that is assessed as likely related to study drug

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

Subjects who discontinue treatment with study drug prior to completing the treatment period will have a Follow-up visit 28 days after their last dose of study drug (see Section 6.5.11). Every effort should be made for subjects to complete the Follow-up visit after a subject has discontinued from study drug.

5.7 Concomitant and Excluded Therapies

Concomitant therapies include any therapies (including over-the-counter medications) used by a subject from initiation of study drug treatment through the follow-up period. A record of all medications used will be maintained for each subject throughout the study. Reported information will include a description of the type of drug, treatment period, dosing regimen, the route of administration, and drug indication.

5.7.1 Allowed Therapies

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

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

5.7.2 Excluded Therapies

The following therapies are excluded from 1 week prior to the Baseline Visit (Day 0) through the follow-up period:

- Opioids (including codeine). Opioids (including codeine), if required for other indications, are permitted provided that subjects are receiving a stable dose for at least one week prior to the Baseline Visit (Day 0) and still experiencing a troublesome cough. Subjects must remain on a stable dose for the duration of the treatment period.

The following cough therapies are excluded from 2 weeks prior to the Baseline Visit (Day 0) through the end of the treatment period:

- Dextromethorphan
- Guaifenesin
- Chlorpheniramine maleate extended release tablets
- Benzonatate

The following therapies are excluded from 2 weeks prior to the Baseline Visit (Day 0) through the follow-up period:

- Pregabalin, gabapentin, thalidomide, or amitriptyline for the treatment of cough. Pregabalin, gabapentin, thalidomide, or amitriptyline if required for other indications, is permitted if subjects are receiving a stable dose and still experiencing a troublesome cough. Subjects must remain on a stable dose for the duration of the treatment period.

The following therapies are excluded from 4 weeks prior to the Baseline Visit (Day 0) through the follow-up period:

- Systemic immunosuppressive/immunomodulatory therapies (including but not limited to PDE4 inhibitors, cyclosporine, mycophenolate-mofetil, methotrexate, azathioprine, or phototherapy)
- Strong CYP3A4 inhibitors (See Appendix B)
- Any investigational therapy

The following therapies are excluded from 8 weeks prior to the Baseline Visit (Day 0) through the follow-up period:

- Biologic therapies
- Investigational biologic therapies

The following therapy is excluded from 12 weeks prior to the Baseline Visit (Day 0) through the follow-up period:

- Treatment with an ACE-inhibitor

5.7.3 Use of Excluded Therapies During the Treatment Period

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

5.8 Assignment to Treatment

5.8.1 Randomization

Eligible subjects will be randomized to receive serlopitant 5 mg or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified by country and gender.

An IWRS will be used to perform the randomization.

5.8.2 Blinding

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

5.9 Treatment Compliance

Records of study drug used, dosages administered, and intervals between visits will be kept during the study. Dosing dates and times will be recorded. Subjects will be asked to return all partially used and empty bottles to the study site at each visit. The site staff will count and record the number of remaining tablets in each returned bottle. The site staff will assess the subject's compliance with dosing by reviewing the subject's dosing diary (available on the IWRS website) and the number of remaining study drug tablets relative to the number of days since the bottle was dispensed. A subject who has deviated significantly from the once-daily dosing regimen will be counseled.

6 STUDY SCHEDULE AND ASSESSMENTS

6.1 Efficacy Parameters

6.1.1 Objective Cough Frequency

Objective cough frequency will be measured as 24-hour sound recordings as outlined in Appendix A using a custom-built digital recording device (VitaloJAK, Vitalograph, Ltd).

6.1.2 Cough Severity Visual Analogue Scale (VAS)

A cough severity VAS scored on a 100mm visual analogue scale will be measured at the time points outlined in Appendix A.

6.1.3 Leicester Cough Questionnaire (LCQ)

The LCQ is a cough specific quality of life assessment that will be completed at the time points outlined in Appendix A.

6.1.4 Patient's Global Impression of Change (PGIC)

The PGIC is an instrument used by subjects to assess their overall status since the start of the study. It consists of a 7-point scale ranging from 'very much improved' to very much worse'. The PGIC will be assessed at the time points outlined in Appendix A.

6.1.5 Clinician's Global Impression of Change (CGIC)

The CGIC is an instrument used to assess subjects' overall status since the start of the study. It consists of a 7-point scale ranging from 'very much improved' to very much worse'. The CGIC will be assessed at the time points outlined in Appendix A.

6.2 Safety Parameters

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

6.2.1 Vital Signs

Vital signs will include measurements of heart rate, sitting blood pressure, respiration rate, and temperature. Vital signs will be assessed as outlined in Appendix A and at unscheduled study visits when clinically indicated. The subjects' height and weight will be measured as outlined in Appendix A.

6.2.2 Physical Examination

Physical examinations will be performed as outlined in Appendix A and at unscheduled study visits when clinically indicated.

6.2.3 Clinical Laboratory Assessments

Samples for hematology, chemistry, urinalysis, and serum pregnancy testing (when necessary) will be collected as outlined in Appendix A and at unscheduled study visits when clinically indicated, and analyzed at a central laboratory unless otherwise specified. Detailed instructions regarding sample collection, preparation, and shipment can be found in the laboratory manual. Laboratory assessments will include the following:

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

6.2.4 Electrocardiogram

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

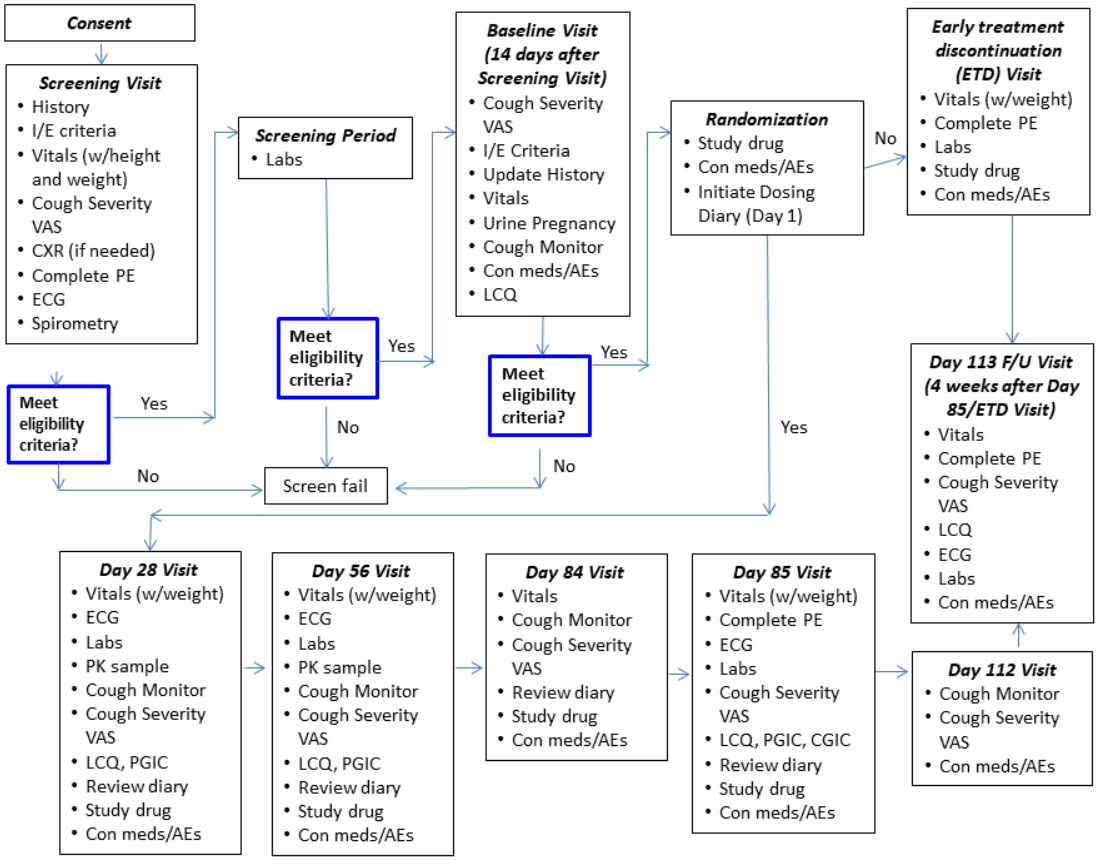
6.3 Pharmacokinetics Measurements

PK samples will be collected at the time points outlined in Appendix A. The date and time of dosing prior to PK sample collection and date and time of PK sample collection will be recorded in the eCRF. Detailed instructions regarding PK sample collection, preparation, and shipment can be found in the laboratory manual.

6.4 Subject Flow Diagram

The visit schedule and assessments are summarized in Appendix A. The following subject flow diagram provides a summary of assessments and decision points for each subject. The IVRS/IWRS dosing diary is performed throughout the study and is not confined to scheduled visits. Refer to Appendix A for frequency and duration of these assessments.

Figure 1 Subject Flow Diagram



6.5 Study Visits

The following sections describe the procedures and assessments to be performed at each study visit. Details of each procedure and assessment can be found in Sections 6.1, 6.2, and 6.3.

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

The IVRS/IWRS dosing diary is performed throughout the Treatment Period and is not confined to scheduled visits. Refer to Appendix A for frequency and duration of these assessments.

6.5.1 Informed Consent

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

6.5.2 Screening Visit/Period

Screening assessments may be conducted over a 14-day period prior to the Baseline visit. The Screening Period may be extended beyond 14 days if the Medical Monitor requires additional follow-up on findings from any of the Screening assessments.

The following screening procedures are to be performed:

- Inclusion/exclusion criteria review
- Cough severity VAS
- Medical history (including chronic cough history, history of any medications within 30 days prior to Screening and chronic cough treatments within 1 year prior to Screening)
- Complete physical examination
- Vital signs (including height and weight)
- ECG
- Spirometry
- Chest radiograph or CT Thorax (if not done within the past 5 years)
- Contact IWRS to register subject
- Laboratory tests
    - Reproductive endocrine labs for females under 55 years of age at time of consent
    - Serum pregnancy test for females of childbearing potential
    - Endocrine
    - Hematology
    - Chemistry
    - Urinalysis
    - Urine drug screen
- Schedule the Baseline visit

6.5.3 Baseline Visit (Day 0)

At the Baseline visit, the following procedures and assessments are to be performed:

- Inclusion/exclusion criteria review
- Update medical history
- Cough severity VAS
- Randomize (via IWRS) subject if all inclusion and exclusion criteria are met
- Contact IWRS to obtain study drug bottles for Days 1–28
- Distribute study drug bottles in a lock box **for subjects who will NOT return to the clinic for the Day 1 visit**.
- **HOLD the study drug bottles AT THE CLINIC for subjects who will return to clinic for the Day 1 visit.**
- Attach and activate the Day 0 cough monitor (preferably before 10 am)
- Vital signs
- Urine pregnancy test for females of childbearing potential
- LCQ
- Record all concomitant medication use
- Schedule Day 1 visit at clinic or at subject's home
- Schedule Day 28 visit at clinic.

6.5.4 Day 1 Visit

At least 24 hours after the cough monitor had been attached (preferably before 10 am), the following activities will be performed by clinic staff or a mobile research nurse will visit the subject to:

- Measure vital signs (sitting systolic and diastolic blood pressure, pulse, respiration rate, temperature)
- Collect the Baseline cough monitor
- Distribute study drug Days 1–28 bottles **for subjects who have returned to the clinic for the Day 1 visit**
- Administer the first dose of study drug (before 10am)
- Conduct IVRS/IWRS training for dosing diary and instruct subjects to complete each day
- Record all AEs
- Record all concomitant medication use
- Remind subject about Day 28 visit at clinic

6.5.5 Day 14 Visit (Telephone Visit)

The following evaluations will be performed by telephone on Day 14 (± 3 days):

- Review IVRS/IWRS Days 1-13 dosing diary entries
- Instruct subjects to continue recording IVRS/IWRS dosing diary entries for Days 14–28
- Record all AEs
- Record all concomitant medication use

6.5.6 Day 28 Visit

The following procedures and evaluations will be performed at the clinic on Day 28 (± 3 days):

- Cough severity VAS
- LCQ
- PGIC
- Vital signs
- Weight
- ECG (12-lead)
- PK sample

- Study drug dosing
    - Observe AM dose (before 10 am)
- Attach and activate Day 28 cough monitor (**AFTER DOSING**)
    - Cough monitor will be collected the following day by a courier service and delivered to the clinic
- Laboratory tests
    - Hematology
    - Chemistry
    - Urinalysis
    - Urine pregnancy test for females of childbearing potential
    - Urine drug screen
- Study Drug
    - Collect/perform accountability for Days 1–28 bottles
    - Contact IWRS to obtain study drug bottles for Days 29–56 and dispense to subject
- Review IVRS/IWRS Days 1-28 dosing diary entries
- Instruct subjects to continue recording IVRS/IWRS dosing diary entries for Days 29–56
- Record all AEs
- Record all concomitant medication use
- Schedule Day 56 visit at clinic

6.5.7 Day 56 Visit

The following procedures and evaluations will be performed at the clinic on Day 56 (± 3 days):

- Cough severity VAS
- LCQ
- PGIC
- Vital signs
- Weight
- ECG (12-lead)

- PK sample
- Study drug dosing
    - Observe AM dose (before 10 am)
- Attach and activate Day 56 cough monitor (**AFTER DOSING**)
    - Cough monitor will be collected the following day by a courier service and delivered to the clinic
- Laboratory tests
    - Hematology
    - Chemistry
    - Urinalysis
    - Urine pregnancy test for females of childbearing potential
    - Urine drug screen
- Study drug
    - Collect/perform accountability for Days 29–56 bottles
    - Contact IWRS to obtain study drug bottles for Days 57–84 and dispense to subject
- Review IVRS/IWRS Days 29–56 dosing diary entries
- Instruct subjects to continue recording IVRS/IWRS dosing diary entries for Days 57–84
- Record all AEs
- Record all concomitant medication use
- Schedule Day 84 visit at clinic

6.5.8 Day 84 Visit

The following procedures and evaluations may be performed at the clinic or at the subject's home by the mobile research nurse on Day 84 (± 3 days):

- Cough severity VAS
- Vital signs
- Study drug dosing
    - Observe AM dose (before 10 am)
- Attach and activate Day 84 cough monitor (**AFTER DOSING**)

- Study Drug - collect/perform accountability for Days 57–84 bottles
- Review IVRS/IWRS Days 57–84 dosing diary entries
- Record all AEs
- Record all concomitant medication use
- Remind subject about Day 85 Visit at clinic

6.5.9 Day 85/Early Treatment Discontinuation Visit

The following procedures and evaluations will be performed at the clinic on Day 85 or within 7 days of the last dose of study drug for subjects who discontinue study drug treatment early.

At this visit, the following procedures and assessments are to be performed:

- Cough severity VAS
- PGIC
- LCQ
- Vital signs
- Weight
- Collect Day 84 cough monitor
- Complete physical exam
- ECG (12 lead)
- Laboratory tests
    - Reproductive endocrine labs for females under 55 years of age at time of consent
    - Endocrine
    - Hematology
    - Chemistry
    - Urinalysis
    - Urine pregnancy test for females of childbearing potential
    - Urine drug screen
- Contact IWRS to register Day 85 end of treatment visit
- Review IVRS/IWRS Days 57–84 dosing diary entries
- The following will be completed by the Investigator (MD or DO):

- CGIC
- Study drug - collect/perform accountability for Days 57–84 bottles (**early treatment discontinuation visit only**)
- Record all AEs
- Record all concomitant medication use
- Schedule Day 112 visit at clinic or at subject's home
- Schedule Day 113 visit at clinic

6.5.10 Day 112 Follow-up Visit

Subjects will return to the clinic or be visited by a mobile research nurse on Day 112 (± 3 days) for the following procedures and evaluations:

- Cough severity VAS
- Record all AEs
- Record all concomitant medication use
- Attach and activate cough monitor
  - Cough monitor will be collected the following day by a courier service and delivered to the clinic
- Contact IWRS to register the Day 112 Follow-up visit
- Remind subject about Day 113 visit at clinic

6.5.11 Day 113 Follow-up Visit

Subjects will return to the clinic on Day 113 for the following procedures and evaluations:

- Vital signs
- Collect Day 112 cough monitor
- Cough severity VAS
- LCQ
- Contact IWRS to register the Day 113 Follow-up visit
- Complete physical exam
- ECG (12-lead)

- Laboratory tests
    - Reproductive endocrine labs for females under 55 years of age at time of consent
    - Endocrine
    - Hematology
    - Chemistry
    - Urinalysis
    - Urine pregnancy test for females of childbearing potential
    - Urine drug screen
- Record all AEs
- Record all concomitant medication use

6.6 Early Termination

Early termination 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 Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If a subject is willing to provide a reason for withdrawal, this will be recorded in the electronic Case Report Form (eCRF).

7 ASSESSMENT OF SAFETY

7.1 Definitions

7.1.1 Adverse Event

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

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

7.1.2 Serious Adverse Event

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

- Death

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

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

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

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

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

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

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

drug should be recorded as medical history, and abnormal findings that occur after the first dose of study drug should be recorded as AEs.

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

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

7.1.4 Deaths

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

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

7.1.5 Pregnancies and Contraception Requirements

For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal; a postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female.

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

a) All female subjects of childbearing potential must use highly effective contraception, which includes the use of one or more of the following acceptable methods:
    i. Surgical sterilization (e.g., bilateral tubal occlusion or ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
    ii. Total (as opposed to periodic or cyclic) abstinence
    iii. Hormonal contraception associated with consistent inhibition of ovulation; these may include (but are not necessarily limited to) oral, intravaginal, implantable, injectable, or transdermal delivery methods.
        i. Progesterone only oral contraceptives are excluded as a highly effective method, as they do not consistently inhibit ovulation.
    iv. Intrauterine device/system

v. Exclusive monogamous heterosexual intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner

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

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

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

7.2 Methods and Timing for Recording and Reporting Adverse Events

7.2.1 Adverse Event Reporting Period

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

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

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

7.2.2 Eliciting Adverse Events

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

7.2.3 Assessment of Severity

All AEs entered into the eCRF will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03

("Common Terminology Criteria for Adverse Events (CTCAE)" 2010) to describe the maximum intensity of the AE.

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

Table 1 Adverse Event Grading

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

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

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

[c]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 ("Common Terminology Criteria for Adverse Events (CTCAE)" 2010)

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

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

7.2.4 Assessment of Causality

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

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

7.3 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

7.5 Reporting Serious Adverse Events to Regulatory Authorities and Study Investigators

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

7.6 Emergency Unblinding

Emergency unblinding is available 24 hours per day/7 days per week and will be performed via IWRS. 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

Endpoints will be summarized with descriptive statistics by treatment group and visit. For continuous variables, the following information will be presented: n, mean, standard deviation, median, minimum and maximum. For categorical variables counts and percentages will be used.

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

8.1 Decision Rule and Sample Size

The comparisons related to the primary and key secondary endpoints will be done in a hierarchical manner to control the familywise error rate. The testing procedure will start by testing the primary endpoint and then proceed to the key secondary endpoints by following the order as specified in Section 8.9.4.

A total of 170 subjects (85/arm) in 1:1 ratio to serlopitant 5 mg or placebo will provide 90% power to detect a 25% relative reduction (placebo-adjusted ratio of 0.75) in 24-hour objective cough frequency or awake objective cough frequency using a two-sample t-test at a one-sided significance level of 0.05. This assumes that 24-hour cough frequency or awake cough frequency follows a log-normal distribution with a CV of 0.64. This sample size also considers an expected dropout rate of 15%.

The sample size calculations have been performed in nQuery Advisor + nTerim.

8.2 Handling of Missing Data and Excluded Therapy Use

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

In case of missing data for the primary efficacy endpoint, two selected imputation approaches are specified for the sensitivity analyses (Section 8.9.2.1). All other efficacy endpoints, analysis will be conducted based on the observed data only.

8.3 Derivations of Efficacy Variables

The 24-hour cough frequency (coughs per hour) for a specified visit is calculated as:

24-hour cough frequency = (total number of cough events during the monitoring period (24-hour interval))/24

The awake cough frequency (coughs per hour) is defined as below:

Awake cough frequency = (total number of cough events during the monitoring period (24-hour interval) the subject is awake)/(Total duration (in hours) for the monitoring period the subject is awake)

Awake duration (hours) is time between waking up and sleep during the 24-hour monitoring period.

The cough data will contain all cough events occurring during that 24-hour monitoring period as well as the information about "sleep time" and "awake time". Any session with duration of recording < 4 hours will be considered as missing.

In general, each 24-hour session is composed by an awake monitoring period and a sleep monitoring period. If a subject did not wake up before the end of the recording session, it will be assumed that the subject slept for the rest of the session. The session will have missing awake time, and the rest of session will be considered under the sleep monitoring period. For any session with both sleep time and awake time missing, the entire 24-hour session will be considered under the awake monitoring period, unless the session has early termination of recording.

On each collection day, the cough count, the actual cough monitoring duration (in hours), and the coughs per hour will be derived for the total 24-hour period, the awake period, and the sleep period, respectively.

The percent change in 24-hour coughs per hour is defined as below:

Percent change in 24-hour cough frequency =

[(Change from baseline in 24-hour cough frequency×100)/(Baseline 24-hour cough frequency)]

The proportion of participants with ≥ 30% of reduction from baseline in 24-hour cough frequency is the number of participants with ≤-30% change in 24-hour cough frequency divided by the total number of participants with available data.

8.4 Analysis Populations

The FAS will serve as the primary population for the analysis of efficacy data in this study. The FAS consists of all randomized subjects who have taken at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period. Subjects will be analyzed according to the treatment group to which they are randomized.

The safety analysis set will be used for the analysis of safety data in this study. The safety analysis set will consist of all subjects randomized who receive at least one dose of study medication. Subjects will be classified based upon the treatment received. For safety analyses, subjects will be classified based upon the treatment received.

The PK analysis set will consist of all subjects who receive ≥ 1 dose of serlopitant and who have at least 1 post-dose PK blood sample available for analysis.

8.5 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.

8.6 Subject Characteristics

Demographic and other baseline characteristics will be summarized. Duration of chronic cough (years) will be derived as year of informed consent minus year of start date of the chronic cough medical history.

8.7 Concomitant Medications

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

8.8 Treatment Compliance and Extent of Exposure

Percent compliance will be calculated for each subject as below:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should Be on Therapy}} \times 100\%$$

A day within the study will be considered an "On-Therapy" day if the participant takes all required medication. If a subject misses a daily dose, that day is not considered an On-Therapy day.

The duration of exposure for each participant will be evaluated by calculating the number of days on therapy.

Percent compliance and duration of exposure to study medication will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum) for the safety analysis set.

8.9 Efficacy Analyses

8.9.1 Statistical Hypotheses and Tests

The study is designed to evaluate, the efficacy of serlopitant 5 mg relative to placebo. The primary hypothesis for this trial is that serlopitant is superior to placebo with respect to the mean change from baseline in 24-hour cough frequency (on the log scale).

Symbolically, the hypotheses for serlopitant 5 mg compared to placebo can be written as:

H_0: $\mu_{SP,Week\ 12} - \mu_{SP,Baseline} = \mu_{PL,Week12} - \mu_{PL,Baseline}$

H_A: $\mu_{SP,Week\ 12} - \mu_{SP,Baseline} < \mu_{PL,Week\ 12} - \mu_{PL,Baseline}$

where μ_{SP} and μ_{PL} represent the mean values at Week 12 for serlopitant 5 mg and placebo, respectively.

As the primary endpoint, cough frequency, is to be analyzed on the log scale the null hypothesis relates to the ratio of Week 12/Baseline for serlopitant 5 mg being the same as that for placebo, and the alternative hypothesis being that the ratio of Week 12/Baseline for serlopitant 5 mg is smaller than the ratio for placebo.

A family wise error rate will be controlled to adjust for multiplicity for the comparison of serlopitant 5 mg to placebo on the primary and key efficacy endpoints in a hierarchical manner (see details in Section 8.9.4).

8.9.2 Primary Endpoint

The primary efficacy endpoint of this study is change from baseline in 24-hour objective cough frequency at each dose studied after 12 weeks of treatment. A negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

As the change in 24-hour cough frequency may have a skewed and wide distribution, the primary analysis for the primary endpoint will be on the natural log scale of the cough frequency data. The difference between serlopitant 5 mg and placebo will be estimated using a mixed effect repeated measures (MMRM) model. The model will include factors for treatment, visit, country, sex, the treatment-by-visit interaction; and the log-transformed baseline value as a covariate. The MMRM model will use all available 24-hour cough frequency data on Day 28, 56, and 84. An unstructured covariance structure will be applied for MMRM. In case the model will not converge with the unstructured covariance structure, the heterogeneous compound symmetry (CSH) will be used instead. Contrasts will be constructed to compare the serlopitant 5 mg group to the placebo group at each visit.
The least-squares (LS) mean change from baseline (on the log scale) with the associated standard errors will be displayed for each treatment group. Estimated treatment differences (serlopitant vs. placebo) along with corresponding CIs will also be presented.

In addition, the geometric mean of 24-hour cough frequency will be presented by treatment and by visit. The percent difference change between serlopitant and placebo will be estimated

by 100 (e^{diff} - 1), where diff is the difference provided by the analysis of the log-transformed variable.

An observation of zero coughs per hour will be replaced by a cough rate of 0.1/hr for the calculation of geometric means. If this rule is used the table will have a footnote detailing the participant and treatment. Further details of the model specification, assumptions, and SAS implementation codes will be provided in the SAP.

Furthermore, the changes from baseline in 24-hour cough frequency on the original scale will be also analyzed using a the same MMRM model.

8.9.2.1 Sensitivity Analysis

The primary analyses (MMRM) for assessing primary efficacy variable are valid if the missing data are missing at random (MAR), meaning that the probability of a value being missing, conditional on the observed data and factors in the statistical model, is random and not dependent on the unknown value of the missing data point. Therefore, two sensitivity analyses under missingness not at random (MNAR) will be conducted for the primary efficacy variable to evaluate the robustness of efficacy results and the effect of missing data.

Sensitivity analysis using a copy-reference multiple-imputation method will be performed to assess the robustness of the primary analysis based on MMRM. In this sensitivity analysis, intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. This imputation will be done by treatment group, using MI procedure in SAS 9.4. This imputation will be done by treatment group. Then all the monotone missing values will be multiply-imputed using the imputation model built from the control group, i.e., assuming the missing data in the treatment group will have a profile that equals the profile of the control group for all time points (i.e., a copy-reference imputation). The missing data imputation will be implemented using PROC MI in SAS 9.4 with the MNAR statement. The change from baseline values from each of the completed datasets will then be analyzed using MMRM to include terms for treatment and baseline. The results will be combined using SAS PROC MIANALYZE. It is known that this approach may produce an inflated variance estimate for the treatment comparison. To get a correct variance, a pattern mixture model approximation method will also be used. Results from both the MIANALYZE and the pattern mixture model approximation will be presented as sensitivity analyses.

An additional sensitivity analysis using the tipping-point approach will be conducted. The Variant 3 of the tipping point will be applied (Ratitch 2013). The technical details for the sensitivity analyses will be provided in the SAP.

8.9.3 Secondary Endpoints

Key Secondary

- Change from baseline in awake objective cough frequency after 12 weeks (Day 84) of treatment

- Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour at Week 12
- Proportion of subjects with ≥ 30% reduction in awake objective cough frequency per hour at Week 12
- Change from baseline in Cough Severity Visual Analog Scale (VAS) at Week 12

Other Secondary

- Change from baseline in 24-hour objective cough frequency after 4 and 8 weeks (Day 28 and 56) of treatment
- Change from baseline in awake objective cough frequency after 4 and 8 weeks (Day 28 and 56) of treatment
- Change from baseline in 24-hour objective cough frequency at the Follow-Up visit (Day 112)
- Change from baseline in sleep objective cough frequency after 4, 8 and 12 weeks (Day 28, 56 and 84) of treatment
- Change from Baseline in Cough Severity Visual Analog Scale (VAS) at Weeks 4 and 8
- Change from Baseline in Leicester Cough Questionnaire (LCQ) individual Domain and Total scores
- Patient's Global Impression of Change (PGIC)
- Clinician's Global Impression of Change (CGIC)

Statistical approaches for analysis of the secondary endpoints will be detailed in the SAP. The continuous secondary efficacy endpoints will be analyzed using the same MMRM model as used for the primary efficacy analysis.

The categorical secondary efficacy endpoints will be analyzed using the stratified Miettinen and Nurminen (M&N) method, adjusting for gender and country.

Table 2 Analysis Strategy for Primary and Key Secondary Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Efficacy Endpoint			
Change from baseline in 24-hour objective cough frequency after 12 weeks (Day 84) of treatment	MMRM	FAS	Observed data only
			Reference-based imputation & Tipping-point approach
Key Secondary Efficacy Endpoints			
Change from baseline in awake objective cough frequency after 12 weeks (Day 84) of treatment	MMRM	FAS	Observed data only
Proportion of participants with ≥ 30% reduction in 24-hour objective cough frequency after 12 weeks (Day 84) of treatment	Stratified Miettinen and Nurminen (M&N)	FAS	Observed data only
Proportion of participants with ≥ 30% reduction in awake objective cough frequency after 12 weeks (Day 84) of treatment	Stratified Miettinen and Nurminen (M&N)	FAS	Observed data only
Change from baseline in VAS after 12 weeks (Day 84) of treatment	MMRM	FAS	Observed data only

MMRM = Mixed Model Repeated Measures; GLMM= Generalized Linear Mixed Model; VAS = Visual Analogue Scales; FAS = Full Analysis set;

8.9.4 Multiplicity Adjustment

The study is designed to evaluate the efficacy profile of serlopitant 5 mg versus placebo. The sequential testing procedure will be employed to control the overall Type I error rate at 5% with respect to multiple comparisons for the primary and key secondary endpoints. The procedure will be done in a hierarchical manner. The order of the testing is outlined below.

1. Primary endpoint: serlopitant 5 mg versus placebo
2. Key secondary endpoint #1: serlopitant 5 mg versus placebo
3. Key secondary endpoint #2: serlopitant 5 mg versus placebo
4. Key secondary endpoint #3: serlopitant 5 mg versus placebo
5. Key secondary endpoint #4: serlopitant 5 mg versus placebo

First, the test ranked as first will be tested and the difference will be declared statistically significant if the one-sided p value is less than 0.05. Second, in case that the difference for the first comparison is statistically significant, the comparison ranked as second will be tested, and the difference will be declared statistically significant if the one-sided p-value is less than 0.05. The testing will continue as long as the previously ranked objective was statistically significant.

All other efficacy variables will be tested at the 0.05 level of significance without multiplicity adjustment.

8.10 Safety Analyses

8.10.1 Adverse Events

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

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

8.10.2 Clinical Safety Laboratory Results

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

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

8.10.3 Vital Signs

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

8.10.4 Electrocardiograms

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

8.11 Pharmacokinetics Analysis

The PK data and analysis for serlopitant and metabolites will be reported in a PK report that will be a part of the clinical study report.

9 ADMINISTRATIVE ASPECTS

9.1 Changes to the Protocol

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

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

9.2 Study Termination

The Sponsor has the right to terminate this study at any time. Reasons may include, but are not limited to, evidence of a potential safety risk in this study or other serlopitant studies or poor enrollment. 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 form will be provided to the subject.

9.6 Communication with the Institutional Review Board or Ethics Committee

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

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

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

9.7 Disclosure and Confidentiality

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

the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

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

9.8 Records and Electronic Case Report Forms

All study data except central laboratory, PK, IWRS diary, cough counts, 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, and other regulations applicable in the UK.

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 globally.

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 3 Schedule of Visit Activities

Study Procedures	**Screening**	**Baseline**	**Treatment Period**						**Follow-up**	
	Day –14 to Day –1[a,b]	**Day 0**	**Day 1[h]**	**Day 14[k,o]**	**Day 28[k]**	**Day 56[k]**	**Day 84[h,k]**	**Day 85/ETD**	**Day 112[h,k]**	**Day 113**
Written Informed Consent[n]	X									
Inclusion/Exclusion Criteria	X	X								
Demographics; Medical & Medication History	X	X								
Chest Radiograph or CT Thorax[l]	X									
Physical Examination	X							X		X
Vital Signs	X	X	X		X	X	X	X		X
Height & Weight	X				X[m]	X[m]		X[m]		
ECG (12-lead)	X				X	X		X		X
Spirometry	X									
Clinical Laboratory Sampling	X				X[p]	X[p]		X		X
Urinalysis	X				X	X		X		X
Urine Drug Screen	X				X	X		X		X
Serum Pregnancy Test	X									
Urine Pregnancy Test		X			X	X		X		X
PK Sample					X	X				
Attach Cough Monitor		X[g]			X[g]	X[g]	X[f,g]		X[f,g]	
Collect Cough Monitor			X[f]		X[j]	X[j]		X		X
Adverse Event Monitoring			X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
LCQ		X			X	X		X		X
Dosing Diary			Daily during treatment period							
Cough Severity VAS	X	X			X	X	X	X	X	X
Study Drug Distribution and/or Accountability		X[e]	X[c,i]		X	X	X	X[q]		
Review Dosing Diary Entries			X	X	X	X	X	X		
PGIC					X	X		X		
CGIC								X		

Abbreviations: CGIC – Clinician's Global Impression of Change; ECG – electrocardiogram; ETD – early treatment discontinuation; LCQ – Leicester Cough Questionnaire; PGIC – Patient's Global Impression of Change; VAS – visual analog scale.

[a] Multiple clinic visits may be required to complete all screening assessments.

[b] The Screening Period may be extended beyond 14 days if the Medical Monitor requires additional follow-up on findings from any of the Screening assessments.

[c] First dose of study drug administered on Study Day 1 after the cough monitor is removed and before 10am.
[d] To be completed daily during Screening
[e] Study drug is dispensed in a lockbox if subjects do not return to the clinic for Day 1.
[f] May be managed by mobile research nurses.
[g] Cough monitor should be attached before 10am and worn for 24 hours during each assessment.
[h] Visits may be conducted at subject's home (by mobile research nurses).
[i] Mobile research nurses will retrieve the study drug from a lockbox on Day 1.
[j] Cough monitor will be collected by a courier and delivered to the clinic on the following day.
[k] Visit window is ± 3 days.
[l] If not done within the past 5 years.
[m] Weight only
[n] Informed consent must occur prior to any protocol-mandated procedures, including stopping of any excluded therapies. This may occur prior to Day -14.
[o] Telephone visit.
[p] Endocrine and reproductive endocrine tests are not done at Days 28 and 56.
[q] ETD visit only at Day 85.

APPENDIX A (CONT'D)

Table 4 Schedule of Cough Monitoring and Patient Reported Outcomes (PROs)

Cough monitoring devices (VitaloJAK) will be stored at each study center and attached to subjects at the visits shown below. The PROs will be completed within IVRS/IWRS or on paper as shown below. PROs are provided to subjects at the screening visit.

Device	Assessment	Frequency and Duration of Assessment
VitaloJAK	Cough Monitoring	Baseline, Day 28, Day 56, Day 84, Day 112
IVRS/IWRS	Daily dosing	Daily during the 84-day treatment period
Paper	Cough Severity VAS	Once at Screening, Baseline, Day 28, Day 56, Day 84, Day 85, Day 112, Day 113
Paper	LCQ	Baseline, Day 28, Day 56, Day 84, Day 113
Paper	PGIC	Day 28, Day 56, Day 84

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-mediatedmetabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)"):

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

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

APPENDIX C ACCP/BTS GUIDELINES

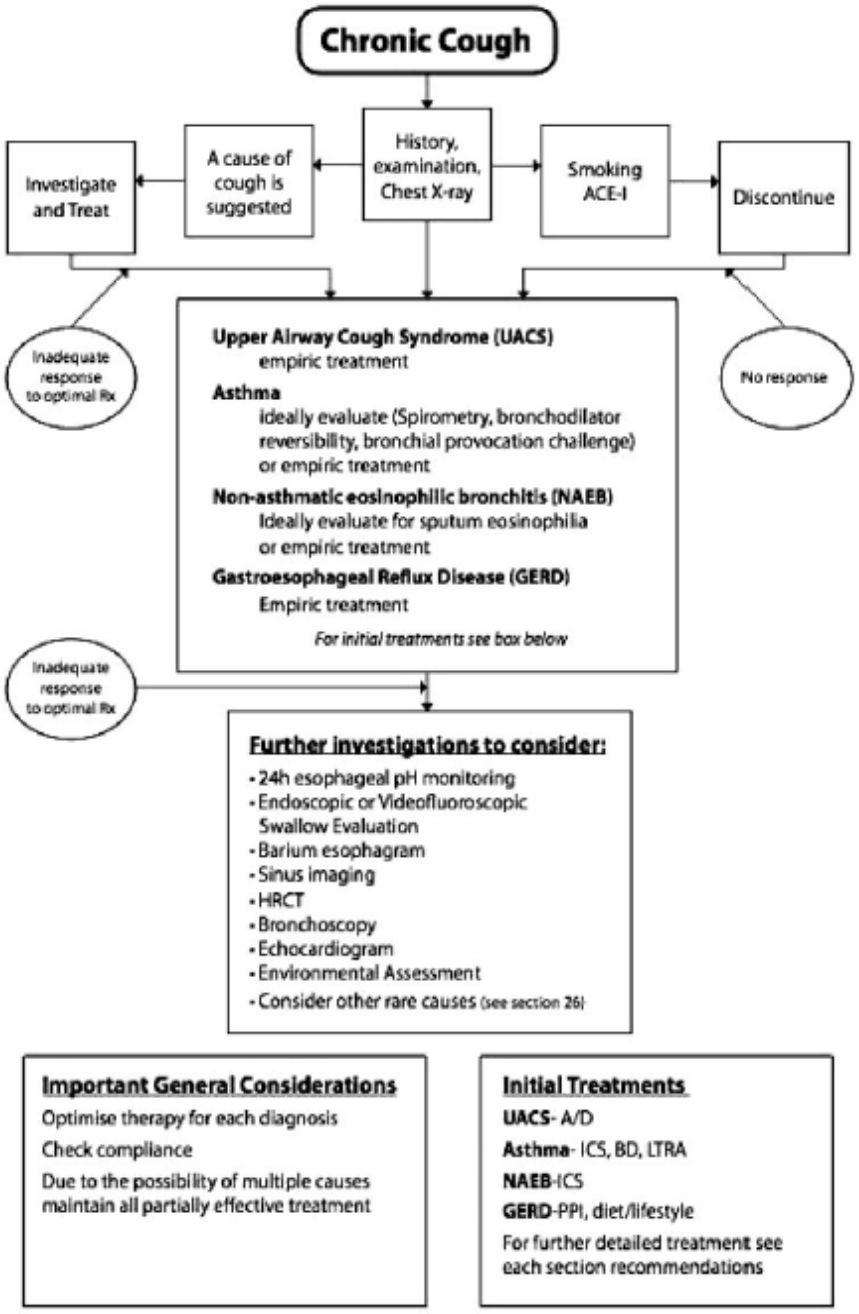

FIGURE 3. Chronic cough algorithm for the management of patients ≥ 15 years of age with cough lasting > 8 weeks. ACE-I = ACE inhibitor; BD = bronchodilator; LTRA = leukotriene receptor antagonist; PPI = proton pump inhibitor. See the legend of Figure 1 for abbreviations not used in the text.