STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Refractory Chronic Cough

Protocol No: MTI-110

Protocol Version / Date: Version 3.0 /08-MAR-2018

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Compound:	MTI
Study Number:	110
Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Serlopitant for the Treatment of Refractory Chronic Cough
Sponsor:	Menlo Therapeutics Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063
Plan Version:	Version 1.0
Version Date:	May 10, 2018
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The signatures below indicate approval of the Statistical Analysis plan for this study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	adverse event
ANCOVA	Analysis of covariance
BMI	body mass index
CGIC	Clinician global impression change
CMH	Cochran Mantel Haenszel
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLMM	Generalized linear mixed model
LCQ	Leicester cough questionnaire
LS Mean	Least-squares mean
M&N	Stratified Miettinen and Nurminen
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
PCI	Potentially Clinically Important
PGIC	Patient global impression change
MI	Multiple imputation
PK	pharmacokinetic (adjective) or pharmacokinetics (singular noun)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
TEAE	treatment-emergent adverse event
VAS	Visual analogue scale
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan (SAP) outlines the data and procedures used for assessing the efficacy, safety, and tolerability of serlopitant from Protocol MTI-110: A Randomized, Parallel, Double-Blind Study to Assess the Efficacy, Safety, and Tolerability of Serlopitant in Subjects with Treatment Refractory Chronic Cough.

2.0 STUDY OBJECTIVE

2.1 Primary Objective:

- 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

2.2 Secondary Objectives

- 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 using Leicester Cough Questionnaire (LCQ)
- To assess the safety and tolerability of repeated oral doses of serlopitant in subjects with treatment refractory chronic cough

3.0 STUDY DESIGN AND PROCEDURES

This is a 12-week randomized, parallel, 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 placebo.

For all subjects, there will be a Screening Period of up to 2 weeks. At the Baseline visit (Study Day -1), eligible subjects will be randomly assigned to one of two treatment groups and will have baseline cough monitoring conducted.

After Baseline, subjects will be entered into a 12-week (84-day) treatment period and 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 28 days after the ETD visit.

Study drug will be administered as follows (Table 1):

Table 1: Treatment Schedule

Study Days	Study Drug Dose
Days 1-84	Serlopitant 5 mg
	Placebo

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 Day 2, subjects will take one tablet per day orally in the morning. Subjects will be instructed to take all doses at approximately the same time each day.

The following assessments will be conducted to evaluate the efficacy of serlopitant:

- Objective Cough Frequency: 24-hour sound recordings at Baseline (Study Day -1) and on Days 28, 56, 84, and 112 using a 510(K) FDA approved and CE-marked digital recording device (VitaloJAK, Vitalograph, Ltd).
- Cough Severity Visual Analogue Scale (VAS): scored on a 100 mm visual analogue scale at Screening, Baseline (Study Day -1), Days 28, 56, 84, 85/ETD, 112, and 113.
- Leicester Cough Questionnaire (LCQ): completed at Baseline (Study Day -1), Days 28, 56, 85/ETD, and Day 113.
- Patient's Global Impression of Change (PGIC): completed at Days 28, 56, 85/ETD
- Clinician's Global Impression of Change (CGIC): completed at Day 85/ETD

Subjects will return 4 weeks after completing the 12-week Treatment Period and Day 85/ETD Visit for Follow-Up Visits Day 112 and Day 113. The visit schedule and assessments are summarized in Appendix B. And, the study visit map is presented in Appendix C.

3.1 Randomization

Subjects will be assigned to one of two treatment groups based on a randomization scheme. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate subjects to randomization numbers. Subjects who meet entry criteria will be randomly assigned to serlopitant 5 mg or placebo in a 1:1 ratio for up to 84 days. Treatment allocation/randomization will be stratified according to the following factors:

- Gender (Male; Female)
- Country (USA, UK)

4.0 INTERIM ANALYSES

No interim analysis planned for this study.

5.0 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Endpoint

The primary efficacy endpoint of this study is:

- Change from Baseline in 24-hour objective cough frequency after 12 weeks (Day 84) of treatment.

The study is designed to evaluate the efficacy profile of serlopitant 5 mg versus placebo. The comparisons between serlopitant 5 mg and placebo related to the primary efficacy endpoint will be done in a hierarchical manner, see Section 8.5.

5.1.2 Key Secondary Endpoints

Key secondary endpoints that will be assessed include:

- 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)

5.1.3 Other Secondary Endpoints

- 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 and change from Day 84 in 24-hr 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 Leicester Cough Questionnaire (LCQ) individual Domain and Total scores
- Patient's Global Impression of Change (PGIC)
- Clinician's Global Impression of Change (CGIC)

5.2 Safety Endpoints

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.

The safety endpoints include:

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Change in clinical laboratory parameters following study drug exposure
- Change in vital signs and ECG parameters following study drug exposure
- Plasma concentrations of serlopitant and metabolites

6.0 ANALYSIS SETS

6.1 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.

6.2 Safety Analysis Set

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.

6.3 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.

7.0 DEFINITION OF VARIABLES

7.1 Baseline

For purposes of assessing changes in vital signs, physical examination results, 12-lead ECG results and clinical laboratory values, baseline refers to the study as a whole and is defined as the last observation prior to the first study treatment. For all efficacy variables, baseline refers to the observation collected at Baseline visit (Study Day -1).

7.2 Study Day

Study Day 1 is the date of first study medication. Study Day relative to Study Day 1 will appear in the listings where applicable.

If the date of event is on or after the 1st study medication date then

Study Day = date of event – date of 1st study medication +1

If the date of event is prior to the first study medication then:

Study Day = date of event – date of 1st study medication

7.3 Analysis Windows

The analysis windows used to report cough frequency endpoints are outlined in Table . If more than one assessment is available within the range the assessment closest to the target day is reported for the analyses window. If two observations exist with the same distance to the target day, the first observation is used.

Table 2: Analysis Windows

Analysis Visit	Range	Target Day
Baseline	Day ≤1	Day 1
Day 28 (Week 4)	Day 2 to Day 42	Day 28
Day 56 (Week 8)	Day 43 to Day 70	Day 56
Day 84 (Week 12)	Day 71 to min (Day 91, TRTEDT+7)	Day 84
Day 112 (Follow-Up)	> min (Day 91, TRTEDT+7)	Day 112

+TRTEDT – date of last study medication

The Follow-Up assessment will be the last assessment available that is at least seven days after the end of treatment. Should no post treatment assessments be available the subject will not have a follow-up assessment. Any assessments reported after the date of last study medication will be considered as a follow-up assessment.

For other efficacy and safety endpoints, the study visits as specified in the protocol will be utilized as analysis visits.

7.4 Age

Age will be derived as date of informed consent minus date of birth then divided by 365.25 and presented in years.

7.5 Duration of Chronic Cough

Duration of chronic cough (years) will be derived as year of informed consent minus year of start date of the chronic cough medical history.

7.6 Prior and Concomitant Medications

Prior medications are all those medications that are not concomitant (for which there is enough information to determine that the medication was stopped prior to the first dose of study treatment). Concomitant medications are those medications that begin after the first dose of study treatment or are present at baseline but continue after the first dose of study treatment. Medications missing both start and stop dates or having a start date prior to the start of study treatment and missing stop date will be counted as concomitant medication.

8.0 GENERAL STATISTICAL CONSIDERATIONS

The statistical software package SAS® Version 9.4 or higher (SAS Institute, Cary, NC, USA) will be used to perform all analyses and to summarize data.

8.1 General Analysis Considerations

For continuous variables, descriptive statistics will include the number of subjects reflected in the calculation (n), mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized using frequency counts and percentages. Treatment differences in response rates (e.g., proportion of cough frequency responders) will be estimated using the stratified Miettinen and Nurminen (M&N) method (stratified by country and sex). Treatment differences in continuous data collected over multiple study visits (e.g., changes from baseline in awake cough frequency) will be assessed using the MMRM model with treatment, visit (nominal time point), country, sex, and the visit by treatment interaction as fixed effects, and baseline value as covariates.

Individual subject data obtained from the electronic case report forms (eCRFs), central laboratory, cough monitoring data, diary data, and any derived data will be presented by subject in data listings to facilitate the investigation of tabulated values and to allow for the clinical review. In general, all tables will be presented by treatment group and listings will be displayed by sorted unique subject identifier and treatment group. A subject identification number is defined as a 3-digit site number followed by a 3-digit sequentially assigned subject id (xxx-xxx). The treatment group in the listings will be based on the planned treatment(s) as allocated by the randomization scheme.

All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as "< 0.0001", a p-value rounding to 1 will be displayed as "> 0.9999". Unless otherwise specified all summaries will be performed by treatment group, all efficacy analyses will be based upon the FAS and all safety analyses will be based upon the Safety Analysis Set. Demographic and baseline characteristic analyses will be based upon the FAS, Safety All Randomized Subjects. The safety and demographic tables will include a total column along with the treatment columns.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses not described herein performed subsequent to database lock will be considered post hoc and exploratory.

8.2 Determination of 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.

8.3 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 24-hr cough frequency and the awake cough frequency, two selected imputation approaches are specified for the sensitivity analyses (Section 9.6.5).

8.4 Data Handling Rules for Cough Analysis

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

24-hour cough frequency = (total number of cough events over 24-hour monitoring period)/ Total duration (in hours) over 24-hour monitoring period

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

Awake cough frequency = (total number of cough events during the monitoring period the subjects 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. Repeated monitoring may be conducted when there is an equipment failure or an unacceptable evaluation from the initial monitoring.

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 at each specific visit 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)]

8.5 Adjustments for Covariates

The primary endpoint will be evaluated using a mixed effect repeated measures (MMRM) model which includes fixed effects for treatment group, visit, country, sex, the treatment-by-visit interaction, and the baseline value as a covariate. In addition, exploratory analysis of the primary endpoint will be conducted by adjusting additional covariates such as age and duration of cough in the MMRM model.

8.6 Examination of Subgroups

Analysis for the primary efficacy endpoint will be provided for the following subgroups of baseline factors:

- Sex (Male, Female);
- Country (USA, UK);
- Age group (18 to 60 years, over 60 years);
- Duration of cough (≥10, <10 in years);
- Baseline 24-hr cough frequency (≥10, <10 in coughs/hour).

For each subgroup, the similar mixed effect repeated measures (MMRM) model as the primary efficacy endpoint will be performed (Section 9.6.2.1) by subgroup variable. Descriptive summary

statistics including mean, SD, and 95% CIs will be also provided. Subsequently, subgroups may be identified on a data-driven basis, and such analyses will be considered exploratory and hypothesis generating only.

8.7 Multiplicity Adjustments

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 hypothesis testing procedure will be done in a hierarchical order as specified below:

- H_1: Change from baseline in 24-hour objective cough frequency after 12 weeks (Day 84) of treatment.
- H_2: Change from baseline in awake objective cough frequency after 12 weeks (Day 84) of treatment
- H_3: Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour at Week 12 (Day 84)
- H_4: Proportion of subjects with ≥ 30% reduction in awake objective cough frequency per hour at Week 12 (Day 84)
- H_5: Change from Baseline in cough severity visual analog scale (VAS) at Week 12 (Day 84)

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.

9.0 STATISTICAL ANALYSES

9.1 Subject Disposition

The disposition of subjects will be summarized by treatment group. The number and percentage of subjects who completed the study and the number and percentage of subjects who were withdrawn will be presented. Subjects who discontinued prematurely will be summarized by number and percentage by reason for discontinuation as specified in the eCRFs.

Protocol deviations will be listed.

9.2 Eligibility Assessments

Subject's eligibility assessments will be listed.

9.3 Demographic and Baseline Information

9.3.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall. Variables include sex, age, ethnicity, race, height, weight, body mass index (BMI), and duration of chronic cough (years).

9.3.2 Medical History

Medical history will be listed and summarized.

9.3.3 Screening Laboratory Tests

Serum pregnancy test and urine drug screen data will be listed. A list of urine drug screen tests is displayed in Appendix D.

9.4 Prior and Concomitant Medication

Prior and concomitant medications will be coded to anatomical therapeutic class and preferred name using the WHO drug dictionary. Listings and tabular summary of prior and concomitant medications will be presented.

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO Drug B2 DDE 2017-09-01)

For the medications recorded on CRF page "Prior and Concomitant Medications", medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing will be considered concomitant medications.

Prior medications and concomitant medications will be presented in tabular form using the ATC Level 2 (pharmacological subgroup) and preferred term (PT). Frequencies and percentages will be presented by treatment group and overall. The tables will be sorted by overall descending frequency of ATC Level 2, and then, within an ATC Level, by overall descending frequency of PT.

Partial or Missing Medication Start and Stop Dates

If the medication start date is incomplete, then it will be imputed as follows for the purpose of determining concomitance only:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining concomitance only:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

The aforementioned missing or partial data handling rules will be applied to the summary tables. The recorded missing or partial date values will be presented in the listings.

9.5 Study Treatment Exposure and Adherence

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.

Overall treatment adherence (%) will be also calculated as below:

Overall treatment Adherence (%) = 100% * (Total number of tablets dispensed - Total number of tablets returned) / Total expected number of tablets taken during the treatment period

The duration of exposure to study medication for each participant will be evaluated by calculating the number of days on therapy. Duration of exposure, percent compliance, and overall treatment adherence (%) will be summarized by treatment group using descriptive statistics (mean, SD, median, minimum, and maximum) for the safety analysis set.

9.6 Efficacy Analyses

For efficacy endpoints, the analysis on FAS will be considered as the primary analysis.

9.6.1 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 8.5). One-sided p-values at 0.05 significance level will be used.

9.6.2 Primary Endpoint

The primary endpoint of the study is the change from baseline in 24-hour objective cough frequency after 12 weeks (Day 84) of treatment.

Cough monitoring is conducted for Baseline (Study Day -1) and 24 hours after administration of the study drug on Days 28, 56, 84, and 112. An independent cough monitoring analysis center

will provide documentation of the time of each cough event over the 24-hour period, as well as the time when the subject goes to sleep and the time the subject awakens.

A negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency. The Baseline cough frequency is derived from the cough monitoring performed at Baseline Visit (Study Day -1), and the post-dose cough frequency is derived from the cough monitoring performed on Days 28, 56, 84, and 112. Change from baseline and percent change in 24-hour objective cough frequency will be calculated for each visit. For descriptive summary only, the percent change from baseline will be capped at 200% for any value > 200%.

9.6.2.1 Analyses of Primary Endpoint

A. <u>Primary Analysis - Mixed Model Repeated Measures Analysis of Log Transformed 24-hour Cough Frequency:</u>

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 fixed effects for treatment group, 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. Furthermore, if the model fails to converge with CSH, the heterogeneous Toeplitz structure (TOEPH) will be used. If the unstructured covariance structure will be used, the denominator degrees of freedom will be computed using the Kenward-Roger method. In case of other covariance structures, the BETWITHIN (SAS®) option will be used for the denominator degrees of freedom. Contrasts will be constructed to compare each of the three serlopitant treatment groups 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 one-sided 95% CIs and p-values will also be presented at each post-baseline timepoint.

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. A sample of SAS code for MMRM analysis is provided in Appendix A.

An observation of zero coughs per hour will be replaced by a cough rate of 0.1 for the calculation of geometric means.

Missing data, in the assessment of the primary hypothesis, is assumed as missing at random (MAR). This assumption will be assessed with a missing data sensitivity analysis (see Section 9.6.5 Sensitivity analysis of the primary endpoint).

B. Secondary Analysis - Mixed Model Repeated Measures Analysis of 24-hour Cough Frequency on the Original Scale:

The changes from baseline in 24-hour cough frequency on the original scale will be also analyzed using the same MMRM model, fitting terms for treatment group, visit, country, sex, the treatment-by-visit interaction, and the Baseline value as a covariate. The least-squares (LS) mean change from baseline (on the original scale) with the associated standard errors will be displayed for each treatment group. Estimated treatment differences (serlopitant 5 mg vs. placebo) along with corresponding one-sided 95% CIs and p-values will also be presented for each treatment group at each post-baseline timepoint. This analysis will be considered as secondary analysis for primary endpoint.

C. Secondary Analysis - ANCOVA Analysis on Ranks of Log Transformed 24-hour Cough Frequency at Week 12:

Additionally, the ranked scores of the primary endpoint (on the natural log scale) at Week 12 (Day 84) will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment group, visit, country, sex, and the log-transformed baseline value as a covariate. This analysis will be considered as secondary analysis for primary endpoint. A sample of SAS code for ANCOVA analysis for ranked data is provided in Appendix A.

9.6.3 Key Secondary Endpoints

9.6.3.1 Awake Objective Cough Frequency

Analyses for awake objective cough frequency will proceed in the same manner as the analyses indicated in Section 9.6.2.1 above at for the Primary Efficacy endpoint.

9.6.3.2 Cough Frequency Responder Analysis

Two key cough frequency responder endpoints are:

- 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)

The proportion of participants with ≥ 30% of reduction from baseline in 24-hour cough frequency at each specific visit is the number of participants with ≤-30% change in 24-hour cough frequency divided by the total number of participants with available data at the specific visit. Similar definition will be applied for awake cough frequency.

In addition, the exploratory analyses of ≥ 50% of reduction and ≥ 70% of reduction will be conducted for both 24-hour and awake cough frequency.

Moreover, for categorical analysis, three responder variables for 24-hour or awake objective cough frequency will be defined based on the magnitude of the percent change from baseline.

> ≥ 70% Reduction = 1 if Percent Change from Baseline in cough frequency at each visit <= -70.0%; 0 Otherwise
>
> ≥ 50% Reduction= 1 if Percent Change from Baseline in cough frequency at each visit <= -50.0%; 0 Otherwise
>
> ≥ 30% Reduction= 1 if Percent Change from Baseline in cough frequency at each visit <= -30.0%; 0 Otherwise

Note that these responder definitions are not mutually exclusive. In particular, a subject who achieves a 1 for ≥ 70% Reduction, will, by definition, be classified as a 1 for ≥ 50% Reduction and ≥ 30% Reduction. The count and percentage of subjects who meet the responder criteria for ≥70% Reduction, ≥50% Reduction, and ≥30% Reduction will be summarized by treatment group and by visit.

For cough frequency responder endpoint, the primary analysis for the comparison of response rates between each of the serlopitant 5 mg and placebo will be conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country and sex, unless stated otherwise). Missing data will be categorized as discontinued or missing. Furthermore, the differences in proportions between two treatment groups will be estimated using the stratified Miettinen and Nurminen (M&N) method. A sample of SAS code for categorical analysis is provided in Appendix A.

In addition, the responder endpoint will be analyzed by a generalized linear mixed model (GLMM) with treatment, visit, country, sex, and treatment by visit interaction as fixed effects. Visit ordering will be treated as a repeated measure within subjects. The GLMM model will use all available cough frequency data on Day 28, 56, and 84. The least-squares (LS) mean proportions with the associated standard errors will be displayed for each treatment group. Estimated odds ratio (serlopitant vs. placebo) along with corresponding one-sided 95% CIs and p-values will also be presented at each post-baseline timepoint.

9.6.3.3 Cough Visual Analog Scale

Cough Visual Analogue Scale (VAS) scored from 0 to 100 using a 100 mm visual analogue scale will be evaluated at Screening, Baseline (Study Day -1), Days 28, 56, 84, Day 85/ETD, Follow-up (Day 112 and Day 113). Baseline cough VAS is defined as the cough VAS at Baseline (Study Day -1).

Change from baseline of cough VAS score will be analyzed in the same way as that for the primary endpoint as indicated in Section 9.6.2.1 above. To explore the correlation between VAS and 24-hour cough frequency, Scatter plots between VAS and 24-hour objective cough frequency counting will be generated.

9.6.4 Other Secondary Endpoints

The following secondary endpoints are planned for analysis:

9.6.4.1 Sleep Objective Cough Frequency

Analyses for sleep objective cough frequency will proceed in the same manner as the analyses indicated in Section 9.6.2.2 above at for the Primary Efficacy endpoint.

9.6.4.2 Cough Frequency at Follow-Up

In order to assess whether 12 weeks of treatment with serlopitant can delay the return of chronic cough, the observed results, change from Day 84, and change from baseline for 24-hour cough frequency, awake cough frequency, and sleep cough frequency at Follow-up Visit (Day 112) will be also summarized.

9.6.4.3 Leicester Cough Questionnaire (LCQ)

The Leicester cough questionnaire (LCQ) instrument will be assessed at Baseline (Study Day0), Day 28, Day 56, 85/Early Termination, and Follow-up (Day 113). There are three domains in the LCQ instrument: Physical (items 1, 2, 3, 9, 10, 11, 14 and 15), Psychological (4, 5, 6, 12, 13, 16, and 17), and Social (7, 8, 18, 19). For each domain, the domain score (range 1-7) is the sum of individual item score within the domain divided by the number of items in the domain; total LCQ score (range 3-21) is the sum of the three domain scores. Baseline LCQ is defined as the LCQ collected at Baseline (Study Day -1).

For each domain (physical, psychological, and social) and total LCQ score, change from baseline will be analyzed in similar manner as indicated for the primary endpoint in Section 9.6.2.1. Line plots of individual subject baseline and post treatment scores will be generated by treatment group and serlopitant for each domain and total LCQ scores.

9.6.4.4 Patient's Global Impression of Change

The self-report measure Patient's Global Impression of Change (PGIC) reflects a patient's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement. Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The counts and proportions of ordered responses to the subject's global perception of change will be computed for each treatment group on Day 28, Day 56, Day 85/ETD. Proportion of subjects with improvements (either "very much improved" or "much improved" on the PGIC scale) will also be presented. The distribution of responses will be compared between each of the serlopitant treatment groups and placebo using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country and sex, unless stated otherwise).

9.6.4.5 Clinician's Global Impression of Change

The Clinician's Global Impression of Change (CGIC) reflects a clinician's belief about the efficacy of treatment. CGIC has the same 7-point scale like PGIC.

CGIC will be evaluated at Day 85/ETD. Similar analysis for PGIC will be applied for CGIC.

9.6.5 Sensitivity Analysis

The primary analyses (MMRM) for assessing 24-hr cough frequency and awake cough frequency 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 24-hr cough frequency and awake cough frequency 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. The variables to be used in the imputation are treatment, corresponding baseline values, and values observed at all double-blind visits (Days 28, 56, and 84). 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. Once the competed

data sets are formed, the same MMRM analysis model as specified for the primary analysis will be applied to each completed set and the inference drawn using Rubin's combination rules (SAS proc MIANALYZE). While 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. A sample of SAS code for sensitivity analysis using the copy-reference MI method is provided in Appendix A.

An additional sensitivity analysis using the tipping-point approach will be conducted to assess the robustness of the primary analysis approach. If it is plausible that, for the active treatment group, the distribution of missing primary endpoint responses has a smaller expected reduction than that of the corresponding distribution of the observed primary endpoint responses, the conclusion under the MAR assumption should be examined. It is desired to impose a fixed and definite set of quantities to encapsulate the change in efficacy associated with withdrawal (missing) for the active treatment group, and the tipping point multiple imputation analysis as described in Ratitch et al. (2013) will be applied. Tipping point analysis is a means of exploring the influence of missingness on the overall conclusion from statistical inference by positing a wide spectrum of assumptions regarding the missingness mechanism (from less conservative to more conservative). The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified while the result is no longer statistically significant. This imputation analysis used a specified sequence of shift parameters, which adjust the imputed values for observations in the active treatment group. The tipping point can be identified while the result is no longer statistically significant. A sample of SAS code for sensitivity analysis using the tipping-point method is provided in Appendix A.

For both sensitivity analyses, the multiple imputations will be completed before log-transforming data.

9.7 Safety Analyses

The safety analysis will utilize the Safety Analysis Set.

9.7.1 Adverse Events

Adverse events will be mapped to system organ classes and preferred terms using the MedDRA dictionary version 20.1. All adverse event summaries will be restricted to treatment emergent adverse events (TEAE), which are defined as those AEs occurring on or after dosing and those

existing AEs worsening during the study. Only treatment-emergent adverse events will be included in the summary tables.

For all AE tables, counting will be by subject and not by event. In other words, if a subject has more than one event with the same preferred term, the subject will be counted once for that preferred term in the treatment group. If a subject has more than one event in the same system organ class, the subject will be counted once for that system organ class in the treatment group.

An overall summary of AEs will be presented. The overall summary will include the number and percentage of subjects experiencing any AEs, study drug related AEs, AEs by maximum severity (highest toxicity grade), SAEs, study drug related SAEs, discontinued due to AE, and deaths. The number and percentage of subjects experiencing each AE, study drug related AE, and SAEs will be summarized by treatment group according to system organ class and preferred term. Additional table including only preferred term summarized by treatment for the number and percentage of subjects experiencing each AE will be presented as well.

Complete subject listings of all AE will be provided. For each AE the following will be specified: treatment group, start and stop dates, severity grade, MedDRA system organ class and preferred term, duration, relationship to study treatment, action taken, outcome of the adverse event and seriousness.

Partial or Missing AE Start and Stop Dates

If the AE start date is incomplete, then it will be imputed as follows for the purpose of determining the onset of AE only:

In the event that the day portion (and only the day portion) of the AE onset date is missing:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.

- If the start day is missing, the day of the first dose date will be used for the event occurring at the same month and year of the first dose date; otherwise, the first day of the month will be used.

- If the start day and month are missing, then the first day of the first month (January) will be used.

If the AE stop date is partial, then it will be imputed as follows for the purpose of determining the duration of AE only:

- If the stop date is completely missing and the event is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the day of the last study day will be used for the event stopping at the same month and year of the last study day; otherwise, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

The aforementioned missing or partial data handling rules will be applied to the summary tables. The recorded missing or partial date values will be presented in the listings.

9.7.2 Laboratory Data

Laboratory evaluations will be collected at Screening, Day 28, Day 56, Day 85/ETD, and Follow-Up (Day 113). All laboratory results including hematology, chemistry, endocrinology, reproductive endocrinology, urinalysis, and urine microscopic parameters will be listed (see Appendix D for the list of parameters for each category). The observed results and change from baseline for hematology, chemistry, endocrinology, and reproductive endocrinology will be summarized descriptively by visit and by treatment group. Baseline for laboratory tests is defined as the last assessment performed prior to Day 1 dosing date. Most subjects have Screening visit as baseline.

9.7.2.1 Abnormal Laboratory Results

For each quantitative hematology, chemistry, endocrinology, and reproductive endocrinology (AMH test only) laboratory parameter, observed values will be compared to normal laboratory reference ranges and classified as “Low”(where applicable), “Normal”, “High (if applicable). For each laboratory parameter, a 4x4 contingency table (shift table) will be displayed that summarizes the counts of subjects who were classified as “Low”, “Normal”, “High” or result missing at Baseline vs. “Low”, “Normal”, “High” or result missing at Post-baseline time points, where Post-baseline time points are Day 28, Day 56, Day 85/ETD, and Day 113. Separate shift tables will be generated for each treatment group at each visit. A listing of abnormal laboratory results will be provided.

9.7.3 Physical Examination

Physical examination information will be listed.

9.7.4 Vital Signs

Vital signs will be collected at Screening, Baseline (Study Day -1), Day 1, Day 28, Day 56, Day 84, Day 85/ETD, and at Follow-Up (Day 113). Vital signs will be summarized by visit and by treatment group. Variables summarized include, systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (bpm), respiratory rate (per minute), and temperature. Baseline for laboratory tests is defined as the last assessment performed prior to Day 1 dosing date.

9.7.4.1 Potentially Clinically Important (PCI) Findings in Vital Signs

At each post-baseline vital signs assessment, observed vital signs results will be categorized into the categories according to the following criteria (Table 3) of potentially clinically important (PCI) findings. The count and percentage of subjects with vital signs parameters at each category of potentially clinically importance (PCI) will be summarized by treatment group for Day 1, Day 28, Day 56, Day 84, Day 85/ETD, and Follow-Up (Day 113).

Table 3: Potentially Clinically Important (PCI) Criteria for Vital Signs

Parameter	Clinically significant value/change
Pulse rate	≤50 bpm and decrease from baseline ≥20 bpm ≥110 bpm and increase from baseline ≥20 bpm
Systolic BP	≤90 mmHg and decrease from baseline ≥20 mm Hg ≥160 mmHg and increase from baseline ≥20 mm Hg
Diastolic BP	≤50 mmHg and decrease from baseline ≥20 mm Hg ≥105 mmHg and increase from baseline ≥20 mm Hg
Respiration rate	≤8 breaths/min and ≤-30% change from baseline ≥25 breaths/min and≥30% change from baseline

9.7.5 12-Lead Electrocardiograms

Electrocardiograms (12-lead) will be obtained at Screening, Day 28, Day 56, Day 85/ETD, and Follow-Up (Day 113). The observed results and change from baseline will be summarized descriptively by visit and by treatment group. ECG variables include heart rate, PR, QT, QTc, RR intervals and QRS duration. QTcB and QTcF are also calculated. Baseline for laboratory tests is defined as the last assessment performed prior to Day 1 dosing date.

The overall ECG assessment will be summarized by visit and by treatment. The count and percentage of subjects with QTcF > 450, 480 and 500 msec and a change from baseline value > 30 and 60 msec will be summarized by visit and by treatment group.

10.0 REFERENCES

[1] Yuan, Yang C. "Multiple Imputation for Missing Data: Concepts and New Development (Version 9.0)", SAS Institute Inc., Rockville, MD

[2] Rubin, D.B. "Multiple Imputation for Nonresponse in Surveys." New York: John Wiley & Sons. (1987)

[3] Ratitch B, O'Kelly M, Tosiello R. "Missing Data in Clinical Trials: From Clinical Assumptions to Statistical Analysis Using Pattern Mixture Models." Pharm Stat. 2013;12:337-347.

[4] Carpenter J.R, Roger J, and Kenward M.G. "Analysis of Longitudinal Trials with Protocol Deviations: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation." Journal of Biopharmaceutical Statistics (2013) 23:1352-1371

[5] Birhanu T, Lipkovich I, Molenberghs G, Mallinckrodt CH. (2013). "A Multiple Imputation Based Approach to Sensitivity Analyses and Effectiveness Assessments in Longitudinal." Clinical Trials, Journal of Biopharmaceutical Statistics.

[6] Bornkamp, Björn, et al. "Innovative approaches for designing and analyzing adaptive dose-ranging trials." Journal of biopharmaceutical statistics 17.6 (2007): 965-995.

[7] SAS/STAT User's Guide

11.0 APPENDICES

APPENDIX A: SAS SAMPLE CODES

A sample of the SAS code for MMRM analysis is provided as below:

```
/*GENERATE LOG-TRANSFORMED COUGH FREQUENCY FIRST*/

PROC MIXED DATA=LOGEFF METHOD=REML;
CLASS TRT01PN USUBJID AVISITN COUNTRY SEX;
MODEL LCHG = TRT01PN AVISITN COUNTRY SEX TRT01PN*AVISITN LBASE / DDFM=KR;
/*LCHG AND LBASE ARE BASED ON THE LOG-TRANSFORMED COUGH FREQUENCY*/
REPEATED / SUBJECT=USUBJID (TRT01PN) TYPE=UN;
LSMEANS TRT01PN*AVISITN / CL PDIFF;
   ESTIMATE 'TRT S - P ON DAY 28' TRT01PN -1 1
                  TRT01PN*AVISITN -1 0 0 1 / CL LOWER LOWERTAILED;
   ESTIMATE 'TRT S - P ON DAY 56' TRT01PN -1 1
                  TRT01PN*AVISITN 0 -1 0 0 1 / CL LOWER LOWERTAILED;
   ESTIMATE 'TRT S - P ON DAY 84' TRT01PN -1 1
                TRT01PN*AVISITN 0 0 -1 0 0 1 / CL LOWER LOWERTAILED;
RUN;
```

Where TRT01PN = planned treatment group in numeric (**1 = placebo, 2 = serlopitant 5 mg**; AVISITN = time point (i.e. Day 28, Day 56, and Day 84); COUNTRY (USA, UK); SEX (Female, Male); TRT01PN*AVISITN = treatment by visit interaction; CHG = hourly cough frequency (on the log scale) – BASE (on the log scale); BASE = baseline hourly cough frequency (on the log scale); TYPE=UN specifies unstructured covariance matrix structure; METHOD=REML specifies the estimation method (REML is the default method); and DDFM=KR requests the Kenward-Roger method for the covariance matrix of the fixed-effect parameter estimates and denominator degrees of freedom for t and F tests.

A sample of the SAS code for ANOVA analysis of ranked 24-hour cough frequency at Week 12 (Day 84) is provided as below:

```
PROC RANK DATA= ADCF OUT=W12_RANK;
 WHERE AVISIT=7;
 RANKS CHG_RANK;
 VAR CHG; /*CHG AND BASE ARE BASED ON THE LOG-TRANSFORMED COUGH FREQUENCY*/
RUN;
PROC MIXED DATA=W12_RANK METHOD=REML;
CLASS TRT01PN USUBJID COUNTRY SEX;
MODEL CHG_RANK = TRT01PN COUNTRY SEX BASE / DDFM=KR;
/*CHG AND BASE ARE BASED ON THE LOG-TRANSFORMED COUGH FREQUENCY*/
LSMEANS TRT01PN / CL PDIFF;
   ESTIMATE 'TRT S - P ON DAY 84' TRT01PN -1 1
                  / CL LOWER LOWERTAILED;
RUN;
```

A sample of the SAS code for CMH and M&H is provided as below:

```
SAS PROC FREQ procedure will be used. CRIT1FN is the response variable = '1'
(i.e. non-responder as the reference level).

PROC SORT DATA=ADAMDATA.ADCF OUT=ADCF;
BY USUBJID AVISITN;
WHERE PARAMCD=' XXXXX' AND DTYPE='' AND AVISITN = x;
RUN;

/*Treatment comparison using stratified CMH*/
PROC FREQ DATA=ADCF;
   TABLES COUNTRY* SEX* TRT01PN* CRIT1FN/CMH
                    alpha=0.1 ;
   weight Count;
run;

/*Estimate difference in proportions (Serlopitant – Placebo) by Country*/
PROC FREQ DATA=ADCF;
   TABLES COUNTRY* TRT01PN* CRIT1FN/ riskdiff (cl= MN CORRECT)
                    alpha=0.1 ;
   weight Count;
run;

/*Estimate difference in proportions (Serlopitant – Placebo) by Sex*/
PROC FREQ DATA=ADCF;
   TABLES SEX* TRT01PN* CRIT1FN/ riskdiff (cl= MN CORRECT)
                    alpha=0.1 ;
   weight Count;
run;

/*Estimate difference in proportions (Serlopitant – Placebo) by Country and by
Sex*/
PROC FREQ DATA=ADCF;
   TABLES COUNTRY* SEX* TRT01PN* CRIT1FN/ riskdiff (cl= MN CORRECT)
                    alpha=0.1 ;
   weight Count;
run;
```

A sample of the SAS code for GLMM analysis is provided as below:

```
PROC SORT DATA=ADAMDATA.ADCF OUT=ADCF;
BY USUBJID AVISITN;
WHERE PARAMCD=' XXXXX' AND DTYPE='' AND AVISITN>0;
RUN;

PROC GLIMMIX DATA=ADCF;
CLASS TRT01PN USUBJID AVISITN COUNTRY SEX;
MODEL CRIT1FN (EVENT='1') = TRT01PN AVISITN TRT01PN*AVISITN COUNTRY
/ LINK=LOGIT DIST=BINARY ODDSRATIO (DIFF=FIRST);
```

```
RANDOM _RESIDUAL_ / SUBJECT=USUBJID (TRT01PN) TYPE=UN;

/*LS-mean estimates and SEs for proportions Serlopitant vs. placebo*/
LSMEANS TRT01PN*AVISITN / ILINK CL ;

/*Estimates of odds ratio (Serlopitant vs. placebo) and CI at each post-
baseline visit*/
ESTIMATE 'TRT 5mg / P' TRT01PN -1 1,

       'TRT 5mg / P ON DAY 28' TRT01PN -1 1
                     TRT01PN*AVISITN -1 0 0 1,
       'TRT 5mg / P ON DAY 56' TRT01PN -1 1
                   TRT01PN*AVISITN 0 -1 0 0 1,
       'TRT 5mg / P ON DAY 84' TRT01PN -1 1
                   TRT01PN*AVISITN 0 0 -1 0 0 1 / EXP CL UPPER UPPERTAILED;
 RUN;
```

A sample of the SAS code for sensitivity analysis using the copy-reference MI method is provided as below:

```
/*Generate transpose of adcf - wide format before Step 1*/
/*---- Generates 10 imputed data sets based on original (non-transformed)
data----*/
 /*Step 1: Achieve Monotone Missing Data Pattern */
  PROC MI DATA=&DATA SEED=14823 NIMPUTE=10 OUT=MONO;
       /* Use numeric TRT01PN */
     VAR BASE AVAL1 AVAL2 AVAL3; /*Refer to AVAL at Visits 5, 6, and 7*/
     MCMC IMPUTE=MONOTONE NBITER=5000 NITER =5000;
   BY TRT01PN;
  run;

 /*Step 2: Achieve Control-Based Copy-Reference Imputation */

  PROC MI DATA=MONO SEED=14823 NIMPUTE=1 OUT=OUTM1;
      CLASS TRT01PN;
      By _IMPUTATION_;
      VAR TRT01PN BASE AVAL1 AVAL2 AVAL3;
      MONOTONE REG (AVAL2 AVAL3);
      MNAR MODEL (AVAL1 AVAL2 AVAL3/ MODELOBS = (TRT01PN = '0'));
        /*Control=Placebo*/
  RUN;
  PROC SORT DATA =OUTM1; BY _IMPUTATION_ TRT01PN USUBJID LBASE; RUN;
  /*Generate transpose of OUTM1 - skinny format before Step 3*/


/*Step 3: Run MMRM Analysis on Imputed Data */

 PROC MIXED DATA=OUTM1 METHOD=REML;
      BY _IMPUTATION_;
 CLASS TRT01PN USUBJID AVISITN COUNTRY SEX;
```

```
 MODEL LCHG = TRT01PN AVISITN COUNTRY SEX TRT01PN*AVISITN LBASE / DDFM=KR;
 /*LCHG AND LBASE ARE BASED ON THE LOG-TRANSFORMED COUGH FREQUENCY*/
 REPEATED / SUBJECT=USUBJID (TRT01PN) TYPE=UN;
 LSMEANS TRT01PN*AVISITN / CL DIFF PDIFF;
      ESTIMATE 'TRT S - P ON DAY 28' TRT01PN -1 1
                  TRT01PN*AVISITN -1 0 0 1 / CL LOWER LOWERTAILED;
      ESTIMATE 'TRT S - P ON DAY 56' TRT01PN -1 1
                  TRT01PN*AVISITN 0 -1 0 0 1 / CL LOWER LOWERTAILED;
      ESTIMATE 'TRT S - P ON DAY 84' TRT01PN -1 1
                TRT01PN*AVISITN 0 0 -1 0 0 1 / CL LOWER LOWERTAILED;
      ODS OUTPUT PARAMETERESTIMATES=PESTIMATES;
RUN;

/*Step 4: Combining estimates from each imputed data set */
 /*First, sort the data of estimates by visit (variable "LABLE") */
PROC MIANALYZE DATA=PESTIMATES;
      MODELEFFECTS ESTIMATE;
      STDERR STDERR;
      BY LABEL;
      ODS OUTPUT PARAMETERESTIMATES= MIPARM;
RUN;
```

A sample of the SAS code for sensitivity analysis using the tipping-point approach is provided as below:

```
     /*-----------------------------------------------------------*/
     /*--- Performs multiple imputation analysis             ---*/
     /*--- for specified shift parameters:                   ---*/
     /*--- data= input data set                              ---*/
     /*--- smin= min shift parameter                         ---*/
     /*--- smax= max shift parameter                         ---*/
     /*--- sinc= increment of the shift parameter            ---*/
     /*--- outparms= output parameters                       ---*/
     /*-----------------------------------------------------------*/


%MACRO MIPARMS( DATA=, SMIN=, SMAX=, SINC=, OUTPARMS=);

DATA &OUTPARMS;
   SET _NULL_;
RUN;

/*------------ # of shift values ------------*/
%LET NCASE= %SYSEVALF( (&SMAX-&SMIN)/&SINC, CEIL );

/*---- Multiple imputation analysis for each shift ----*/
%DO JC=0 %TO &NCASE;
   %LET SJ= %SYSEVALF( &SMIN + &JC * &SINC);

  /*---- Generates 10 imputed data sets ----*/
```

```
  /*Step 1: Achieve Monotone Missing Data Pattern */
  PROC MI DATA=&DATA SEED=14823 NIMPUTE=10 OUT=MONO;
       ** Use numeric TRT01PN ;
     VAR BASE AVAL1 AVAL2 AVAL3; /*Refer to AVAL at Visits 5, 6, and 7*/
     MCMC IMPUTE=MONOTONE NBITER=5000 NITER =5000;
     BY TRT01PN;
  run;

/*Step 2: Impute all visits under MAR first, then apply delta adjustments at
each visit*/
  PROC MI DATA= OUTM1 SEED=14823 NIMPUTE=1 OUT=OUTM2;
      CLASS TRT01PN;
      BY _IMPUTATION_;
      VAR TRT01PN BASE AVAL1 AVAL2 AVAL3;
      MONOTONE REG (AVAL2 AVAL3);
      MNAR ADJUST( AVAL1 / SHIFT=&SJ  ADJUSTOBS=(TRT01PN ='1') );
      MNAR ADJUST( AVAL2 / SHIFT=&SJ  ADJUSTOBS=(TRT01PN ='1') );
      MNAR ADJUST( AVAL3 / SHIFT=&SJ  ADJUSTOBS=(TRT01PN ='1') );
      RUN;
      PROC SORT DATA =OUTM1; BY _IMPUTATION_ TRT01PN USUBJID BASE; RUN;
/*Generate transpose of OUTM2 - skinny format before Step 3*/


/*Step 3: Run MMRM Analysis on Imputed Data */

       PROC MIXED DATA=OUTM2 METHOD=REML;
            BY _IMPUTATION_;
       CLASS TRT01PN USUBJID AVISITN COUNTRY SEX;
       MODEL LCHG = TRT01PN AVISITN COUNTRY SEX TRT01PN*AVISITN LBASE /
       DDFM=KR; /*CHG AND BASE ARE BASED ON THE LOG-TRANSFORMED COUGH
       FREQUENCY*/
       REPEATED / SUBJECT=USUBJID (TRT01PN) TYPE=UN;
       LSMEANS TRT01PN*AVISITN / CL DIFF PDIFF;
       ESTIMATE 'TRT S - P ON DAY 28' TRT01PN -1 1
                  TRT01PN*AVISITN -1 0 0 1 / CL LOWER LOWERTAILED;
       ESTIMATE 'TRT S - P ON DAY 56' TRT01PN -1 1
                  TRT01PN*AVISITN 0 -1 0 0 1 / CL LOWER LOWERTAILED;
       ESTIMATE 'TRT S - P ON DAY 84' TRT01PN -1 1
                 TRT01PN*AVISITN 0 0 -1 0 0 1 / CL LOWER LOWERTAILED;
       ODS OUTPUT PARAMETERESTIMATES=PESTIMATES;
       RUN;
      /*First, sort the data of estimates by visit (variable "LABLE") */
       PROC SORT DATA=PESTIMATES; BY LABEL; RUN:
    /*Step 4: Combining estimates from each imputed data set */
      PROC MIANALYZE DATA=PESTIMATES;
            MODELEFFECTS ESTIMATE;
            STDERR STDERR;
            BY LABEL;
            ODS OUTPUT PARAMETERESTIMATES=MIPARM;
```

```
      RUN;

     DATA MIPARM;
          SET MIPARM;
          SHIFT= &SJ;
     RUN;

           /*----- Output multiple imputation results ----*/
     DATA &OUTPARMS;
            SET &OUTPARMS MIPARM;
          RUN;

          %END;
          %MEND MIPARMS;

/*Assume that the tipping point for the shift parameter that reverses the
study conclusion is between 0 and 100. The following statement performs
multiple imputation analysis for each of the shift parameters 0,10,20,30,…,
100.*/

     ODS LISTING CLOSE;
     %MIPARMS(DATA=XXXX, SMIN=0, SMAX=100, SINC=10, OUTPARMS=PARMS1);


/* Step 5: Finding Tipping Point for Shift Parameter between 0 and 100 such
that p-value is less than 0.05, below is an example for a tipping point for
the shift parameter between 40 and 50.

For a two-sided Type I error level of 0.05, the tipping point for the shift
parameter is greater than 40. The following statement performs multiple
imputation analysis for shift parameters 40, 41, …, 50*/

%MIPARMS(DATA=XXXX, SMIN=40, SMAX=50, SINC=1, OUTPARMS=PARM2);

/*The following statements display the p-values that are associated with the
shift parameters.*/

      PROC PRINT LABEL DATA=PARM2;
         VAR SHIFT PROBT;
         TITLE 'P-VALUES FOR SHIFT PARAMETERS';
         LABEL PROBT='PR > |T|';
         FORMAT PROBT 8.4;
      RUN;
```

APPENDIX B: SCHEDULE OF ASSESSMENTS

MTI-110 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,r]**	**Day 113**
Written Informed Consent[n]	X									
Inclusion/Exclusion Criteria	X	X								
Demographics; Medical & Medication History	X	X[d]								
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 fewer than 14 days. Additionally, the Screening Period may be extended beyond 14 days if the Menlo Therapeutics 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] Medical and medication history only.

[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 (considered to be part of standard of care in the UK).

[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.

[r] Day 112 not required if subject has discontinued treatment early.

APPENDIX C: STUDY VISIT MAP WITH MATCHED INTERVAL ID

Study Visits and Matched Interval IDs in Datasets

Study Procedures	**Screening**	**Baseline**	**Treatment Period**						**Follow-up**	
VISIT	**Screening**	**Day 0 Study Day -1**	**Day 1**	**Day 14**	**Day 28**	**Day 56**	**Day 84**	**Day 85 /ETD**	**Day 112**	**Day 113**
VISITNUM	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Interval ID	**148**	**149**	**150**	**151**	**155**	**156**	**157**	**158**	**159**	**160**
Study Visit Window			1ST DAY DOSING	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Vital Sign Data[a]	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**
Cough Severity VAS Monitoring Data[a]	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**
Telephone Contact Data[a]				**X**						
Cough Monitoring Data[b]		**X**			**X**	**X**	**X**		**X**	

[a] Data collected at visits marked as X. Visit dates will be derived based on the following three datasets: vital sign, cough severity VAS monitoring, and telephone contact. If there is any discrepancy in a visit date, the date recorded in vital sign dataset will be considered as the primary date.

[b]The cough monitoring data has regular visits labeled as Baseline, Day28, Day56, Day84, and Day112, and the repeated visits labeled as Baseline-R, Day28-R, Day56-R, Day84-R and Day112-R. Both regular and repeated records at the specific visit will be included in analysis data. Repeated evaluations are usually due to equipment failures or unacceptable initial evaluations.

APPENDIX D: CLINICAL LABORATORY TESTS

For all lab outputs order parameters as indicated in each category as below:

Hematology	
HGB	Hemoglobin (g/dL)
HCT	Hematocrit (%)
RBC	Erythrocytes (10^6/uL)
WBC	Leukocytes (10^3/uL)
NEUT	Neutrophils (10^3/uL)
NEUTLE	Neutrophils/Leukocytes (%)
LYM	Lymphocytes (10^3/uL)
LYMLE	Lymphocytes/Leukocytes (%)
MONO	Monocytes (10^3/uL)
MONOLE	Monocytes/Leukocytes (%)
EOS	Eosinophils (10^3/uL)
EOSLE	Eosinophils/Leukocytes (%)
BASO	Basophils (10^3/uL)
BASOLE	Basophils/Leukocytes (%)
PLAT	Platelets (10^3/uL)
MCH	Ery. Mean Corpuscular Hemoglobin (pg)
MCHC	Ery. Mean Corpuscular HGB Concentration (g/dL)
MCV	Ery. Mean Corpuscular Volume (fL)

Endocrinology	
TSH	TSH ULTRASENSITIVE (uIU/mL)
CORTISOL	CORTISOL, SERUM RANDOM (ug/dL)
ACTH	ACTH, PLASMA (pg/mL)
T4FR	Thyroxine, Free (ng/dL)

Chemistry	
ALP	Alkaline Phosphatase (U/L)
ALT	Alanine Aminotransferase (U/L)
AST	Aspartate Aminotransferase (U/L)
BILI	Bilirubin (mg/dL)
ALB	Albumin (g/dL)
CA	Calcium (mg/dL)
K	Potassium (mmol/L)
URATE	Urate (mg/dL)
CREAT	Creatinine (mg/dL)
GLUC	Glucose (mg/dL)
SODIUM	Sodium (mmol/L)
MG	Magnesium (mg/dL)
CL	Chloride (mg/dL)
LDH	Lactate Dehydrogenase (U/L)
CHOL	Cholesterol (mg/dL)
HDL	HDL Cholesterol (mg/dL)
LDL	LDL Cholesterol (mg/dL)
TRIG	Triglycerides (mg/dL)
UREAN	Urea Nitrogen (mg/dL)
PHOS	Phosphate (mg/dL)
CPROT	Protein (g/dL)
BICARB	Bicarbonate (mmol/L)

Urinalysis	
APPEAR	Appearance
COLOR	Color
KETONES	Ketones
LEUKASE	Leukocyte Esterase
NITRITE	Nitrites
OCCBLD	Occult Blood
PH	pH
SPGRAV	Specific Gravity
BILI	Bilirubin
GLUC	Glucose
PROT	Protein
UROBIL	Urobilinogen

Reproductive endocrinology (females under 55)	
ESTRDIOL	Estradiol (pg/mL)
FSH	FSH (mIU/mL)
LH	Luteinizing Hormone (mIU/mL)
PROGEST	Progesterone (ng/mL)
AMH	ANTI-MULLERIAN HORMONE (ng/mL)

Urine Microscopic

7BAC	BACTERIA(/HPF)
V7OXC	CA OXALASTE CRYSTALS (/HPF)
7EPIR	EPITHELIAL RENAL (/HPF)
7EPIS	EPITHELIAL SQUAMOUS (/HPF)
7EPIT	EPITHELIAL TRANSITIONAL (/HPF)
V7GRC	GRANULAR CAST (/LPF)
7UHC2	HYALINE CAST (/LPF)
V7RCS	RBC CAST (/LPF)
7URBC	RBCS (/HPF)
V7TPC	TRI PHOSPHATE CRYSTALS (/HPF)
V7UAC	URIC ACID CRYSTALS
V7WAC	WAXY CAST (/LPF)
V7WCS	WBC CAST (/LPF)
7UWBC	WBCS (/HPF)
V7YST	YEAST (/HPF)

Urine Drug Screen

OPIATE	OPIATES
OXYCDN	OXYCODONE
HYDCDN	HYDROCODONE
HYDMRPHN	HYDROMORPHONE
OXMCC	OXYMORPHONE
MORPHINE	MORPHINE
CODEINE	CODEINE

Pregnancy, Qualitative

HCG	Choriogonadotropin Beta (ng/mL)

Urine Pregnancy (reported on eCRF)

Other Tests (Manual Diff W/CALC ABS)

PK (Primary and Secondary)