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August 1, 2022

**To: ClinicalTrials.gov**

This is a cover page to the redacted SAP for APC-004 titled Phase 2 Randomized Double-Blind Placebo-Controlled 3-Period Single-Dose Crossover Study to Evaluate the Safety and Efficacy of Two Doses of AD-109 in Mild to Moderate Obstructive Sleep Apnea.

The APC-004 SAP is associated with NCT04631107.

The following proprietary information was redacted from the SAP for APC-004:

- IND number
- Reference to the CRO (Contract Research Organization).

Sincerely,

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Phase 2 Randomized Double-Blind Placebo-Controlled 3-Period Single-Dose Crossover Study to Evaluate the Safety and Efficacy of Two Doses of AD-109 in Mild to Moderate Obstructive Sleep Apnea

| | |
|---|---|
| Protocol Number: | APC-004 |
| Protocol Version: | 2.0 |
| Protocol Date: | 6 January 2021 |

# STATISTICAL ANALYSIS PLAN

Version 2.0

# Phase 2 Randomized Double-Blind Placebo-Controlled 3-Period Single-Dose Crossover Study to Evaluate the Safety and Efficacy of Two Doses of AD-109 in Mild to Moderate Obstructive Sleep Apnea

## STATISTICAL ANALYSIS PLAN

Version 2.0

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Note that the last signature date is the effective date of the plan.

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## LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| AHI | apnea-hypopnea index |
| AE | adverse event |
| ATC | anatomical, therapeutic, and chemical |
| BMI | body mass index |
| CI | confidence interval |
| eCRF | electronic case report form(s) |
| CRO | contract research organization |
| CSR | clinical study report |
| DSST | digit symbol substitution test |
| EEG | electroencephalogram |
| ECG | electrocardiogram |
| HB | hypoxic burden |
| ICF | informed consent form |
| KSS | Karolinska sleepiness scale |
| LS | least square |
| MedDRA | medical dictionary for regulatory activities |
| mITT | modified intent to treat |
| NAW | number of awakenings |
| NREM | non-rapid eye movement |
| ODI | oxygen desaturation index |
| OSA | obstructive sleep apnea |
| PP | per protocol |
| PSG | polysomnography |
| PT | preferred term |
| REM | rapid eye movement |
| SAE | serious adverse event |
| $SaO_2$ | oxygen saturation |
| SAP | statistical analysis plan |
| SE | sleep efficiency |

| Abbreviation | Definition |
|---|---|
| SOC | system organ class |
| SOL | sleep onset latency |
| TEAE | treatment-emergent adverse event |
| TST | total sleep time |
| WASO | wake after sleep onset |
| WHO | world health organization |

# 1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # APC-004 Version 2.0, dated 06 January 2021, titled "Phase 2 Randomized Double-Blind Placebo-Controlled 3-Period Single-Dose Crossover Study to Evaluate the Safety and Efficacy of Two Doses of AD-109 in Mild to Moderate Obstructive Sleep Apnea." Apnimed is developing the combination of atomoxetine and oxybutynin for the treatment of obstructive sleep apnea (OSA). Initial Phase 2 studies of the combination were conducted with marketed oxybutynin (combination designated AD-036), which is a racemic mixture of R- and S-oxybutynin. Subsequent development is being pursued with R-oxybutynin (combination designated AD-109), a new enantiomerically pure form of oxybutynin which is proposed to have an improved safety and efficacy profile in OSA compared to racemic oxybutynin.

Previous studies of AD-036 provided dose-response efficacy and safety data across a broad spectrum of OSA disease severity. Study APC-004 is designed to extend and confirm these findings to AD-109 in a population with mild-to-moderate OSA, in parallel with other studies of AD-109 planned by Apnimed in moderate-to-severe OSA. Study APC-004 is a randomized, double blind, placebo-controlled, 3-period, single-dose crossover study in patients with mild-to-moderate OSA.

This document details the statistical methods planned to perform the final analyses of this study. The reader interested in detail on study rational, study design, and medical background is invited to refer to the study protocol.

# 2. OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

### 2.1.1. Primary Objective

The primary study objective is to compare the efficacy and safety of a higher dose (atomoxetine 75 mg + R-oxybutynin 2.5 mg; 75/2.5) and lower dose (atomoxetine 37.5 mg + R-oxybutynin 2.5 mg; 37.5/2.5) of AD109 to each other and to placebo in the treatment of mild-to-moderate OSA.

## 2.2. Endpoints

### 2.2.1. Primary Endpoint

The primary efficacy endpoint is change in $\log_{10}$ of Hypoxic Burden (HB) 4% plus one (scored in reference to AHI[4%]), 75/2.5 dose vs. placebo

### 2.2.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

- Change in $\log_{10}$(HB[4%] + 1), 37.5/2.5 dose vs. placebo and vs. 75/2.5
- Change in Apnea Hypopnea Index (AHI) 4%
- Change in Oxygen Desaturation Index (ODI) 4%

- Total time with SaO2 <90%, PSG nights
- Proportion of participants with ≥50% reduction in AHI(4%), HB(4%), and ODI(4%)

### 2.2.3. Tertiary Endpoints

The tertiary efficacy endpoints are as follows:

- Karolinska Sleepiness Scale (KSS) score
- Sleep Quality VAS
- OSA endotype endpoints (Vpassive, Vactive, Muscle Compensation, Loop Gain)
- PSG sleep and arousal parameters
    - Sleep stages distribution and percentage of total sleep time (TST) in the various sleep stages
        - Sleep Efficiency (SE)
        - Wake After Sleep Onset (WASO)
        - Number of Awakenings (NAW)
        - Sleep Onset Latency (SOL)
        - Percentage of total sleep time (TST) spent in sleep stage N1 (Stage N1%)
        - Percentage of TST spent in sleep stage N2 (Stage N2%)
        - Percentage of TST spent in sleep stage N3 (Stage N3%)
        - Percentage of TST spent in sleep stage R (Stage R%)
    - Snoring index
    - Arousal indices (respiratory and spontaneous)
    - Fraction of hypopneas
- Alternate measures of AHI, ODI and HB
    - AHI(4%) in non-rapid eye movement (NREM) sleep
    - AHI(4%) in rapid eye movement (REM) sleep
    - AHI(4%) adjusted for position
    - AHI(3% or arousal)
    - HB(3% or arousals)
    - HB(Total)
    - ODI(3%)

### 2.2.4. Safety Endpoints

The safety endpoints are as follows:

- Vital signs, clinical laboratory assessment, electrocardiogram (ECG)

- Spontaneous adverse events, including the post-dosing period
- Digit Symbol Substitution Test (DSST)
- PSG parameters:
    - Heart rate (HR)
    - Total time with $SaO_2$<90%

# 3. INVESTIGATIONAL PLAN

## 3.1. Study Design

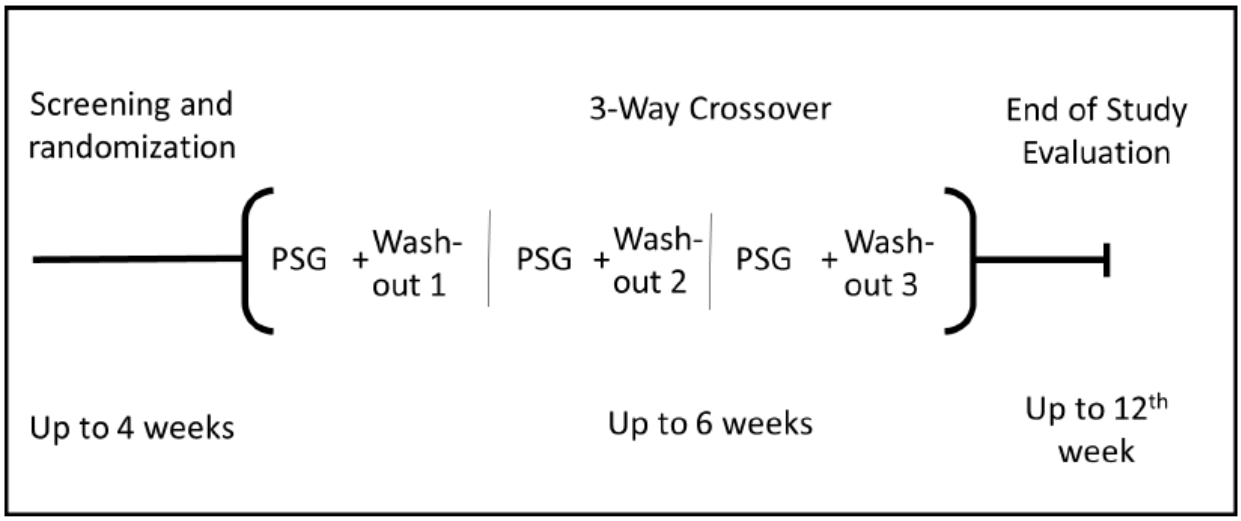
Study APC-004 is a randomized, double blind, placebo-controlled, 3-period, single-dose crossover study in patients with mild-to-moderate OSA. A screening visit and polysomnographic (PSG) exam will be conducted to establish that each participant meets study enrollment criteria. Each participant will then receive a single dose of each of the following during 3 overnight PSG exams, each separated by a one week washout period:

- A: Atomoxetine 75 mg + R-oxybutynin 2.5 mg (i.e., 75/2.5)
- B: Atomoxetine 37.5 mg + R-oxybutynin 2.5 mg (i.e., 37.5/2.5)
- C: Placebo

Efficacy and safety endpoints will compare the 75/2.5 and 37.5/2.5 doses to each other and to placebo.

Each PSG night is followed by a 1-week washout period. Adverse event (AE) and serious adverse event (SAE) information is recorded at each study visit and by telephone contact with participants during each washout period. The overall study duration will be up to 12 weeks (see Figure 1).

*Figure 1: Overview of Study Design*




PSG = polysomnography.

### 3.2. Treatment

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

One tablet of co-formulated atomoxetine and R-oxybutynin or matching placebo is taken immediately before the participant's planned bedtime.

| **Study Treatment Name:** | **Atomoxetine hydrochloride/R-oxybutynin chloride** | **Atomoxetine hydrochloride/R-Oxybutynin chloride** | **Placebo** |
|---|---|---|---|
| **Dosage Formulation:** | Tablet | Tablet | Tablet |
| **Dosage Level:** | 37.5mg / 2.5mg | 75mg / 2.5mg | N/A |
| **Route of Administration:** | Oral | Oral | Oral |
| **Dosing Instructions:** | 1 tablet administered with up to 240 mL water | 1 tablet administered with up to 240 mL water | 1 tablet administered with up to 240 mL water |
| **Storage/Packaging/Labeling:** | Store at room temperature, in HDPE bottles | Store at room temperature in HDPE bottles | Store at room temperature in HDPE bottles |

#### 3.2.1. Randomization Scheme and Treatment Arm Assignment

The planned randomization scheme will utilize randomly ordered blocks with 5 blocks of size 6, with each block randomizing one participant to each of the following 6 sequences: ABC, ACB, BAC, BCA, CAB, CBA. For example, a participant randomized to "ABC" will receive the

treatment sequence: 1.) Atomoxetine 75 mg + R-oxybutynin 2.5 mg; 2.) Atomoxetine 37.5 mg + R-oxybutynin 2.5 mg; 3.) Placebo.

Participants who withdraw from the study will not be replaced.

### 3.2.2. Blinding

The investigator, study personnel and participant will be blinded to the identity of the study drug in all treatment periods. The CRO staff dealing with blinded site study staff will also be blinded. The Sponsor, Medical Monitor, CRO's Drug Safety and Pharmacovigilance staff, as well as site personnel required for drug administration will also be blinded. The centralized PSG technologists will be blinded to treatment assignment.

The CTI unblinded statistician who reviews the production randomization list will be unblinded to the treatment sequence a participant receives; however, this individual will not have access to study data prior to study completion. The investigational pharmacist and/or the study coordinator, depending on the site, will be unblinded to treatment assignment for the purposes of preparing, controlling, dispensing study product and documenting accountability of study product.

### 3.2.3. Dosing Schedule

There are 3 randomized crossover PSG nights. The participant will receive one treatment on each of the 3 PSG nights, separated by at least a one-week washout period. Dosing of the study treatment will occur immediately prior to lights out.

### 3.2.4. Study Treatment Compliance

Only participants enrolled in the study treatments and only authorized site staff may supply or administer study treatments.

After receiving Sponsor approval in writing, sites are responsible for returning all unused or partially used study treatment to the Sponsor or designated third party or for preparing the study treatment for destruction via incineration.

## 4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

In general, continuous variables will be summarized by presenting the set sample size (N), number of participants with available data (n), mean, standard deviation (SD), median, minimum, and maximum. In summaries of change from baseline safety variables, only participants with both baseline and post baseline data will be included. Categorical variables will be summarized by presenting the number and percentage of participants within each category. Calculation of percentages will exclude missing data as a category. Where appropriate, descriptive statistics may be presented with 95% confidence intervals (CIs).

All tabulations will be based on pooled data across centers.

The data analyses will be performed using SAS for Windows, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Covington, KY) will perform the efficacy and safety analyses described below. Apnimed, Inc., will perform the exploratory analysis pertaining to the OSA endotype endpoints mentioned in Section 2.2.3. Any changes to the analyses that are not

included in this SAP will be documented in the clinical study report (CSR).

## 4.1. Data Quality Assurance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis.

Data may be made available to CTI Biostatistics for programming purposes prior to database lock at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis data sets, tables, and listings will be independently programmed by two individuals. The independent SAS outputs produced will be compared, and the SAS programs will be updated until the outputs match.

## 4.2. Analysis Sets

### 4.2.1. Enrolled Set

The Enrolled Set is defined as all participants who signed the informed consent form (ICF) (including screening failures).

### 4.2.2. Modified Intent-To-Treat Analysis (mITT) Set

The mITT Set comprises all participants who are randomized, take at least 1 dose of any of the study treatments, and have at least 1 measurement on the primary endpoint.

Participants will be analyzed for efficacy according to the randomly assigned treatment for each period.

### 4.2.3. Safety Set

The Safety Set consists of all participants who are randomized and receive at least 1 dose of any of the study treatments. Participants will be analyzed for safety based on the treatment received for each period. Treatment received is defined as the actual treatment taken during each period.

### 4.2.4. Per Protocol (PP) Set

The PP Set consists of all participants without any major protocol violations that could influence efficacy assessment. Participants in this set will be analyzed according to the treatment they received for each period.

## 4.3. Assessment Windows

Data will be summarized by the CRF (Study Visit) in which it was collected provided the data is within the windows specified.

## 4.4. Handling of Dropouts or Missing Data

Missing data will remain missing. No imputation of missing data will be performed.

### 4.4.1. PSG Parameters

The criteria for use of PSG data will be as follows:

- When TST is < 120 minutes, only TST, time in bed, Stage N1%, Stage N2%, Stage N3%, and Stage R% will be reported. All other PSG indices will be excluded.
- Any AHI and HB parameters during REM will be reported only when the time spent in REM is > 5 minutes.
- Any AHI and ODI parameters in supine position will be reported only when the time spent supine is > 5 minutes.

### 4.4.2. DSST Scores

A DSST total correct of 0 will be dropped from the repeated measures model.

## 4.5. Multiple Comparisons

Each endpoint for this study implicitly contains three hypothesis tests based on comparisons between study treatments: i) 75/2.5 dose vs placebo, ii) 37.5/2.5 dose vs placebo, iii) 37.5/2.5 dose vs 75/2.5 dose. The sequential testing order of these hypotheses will be:

1. 75/2.5 dose vs placebo for HB(4%),
2. 37.5/2.5 dose vs placebo for HB(4%),
3. 75/2.5 dose vs placebo for AHI(4%),
4. 37.5/2.5 dose vs placebo for AHI(4%),
5. 75/2.5 dose vs placebo for ODI(4%),
6. 37.5/2.5 dose vs placebo for ODI(4%),
7. 37.5/2.5 dose vs 75/2.5 dose for HB(4%),
8. 37.5/2.5 dose vs 75/2.5 dose for AHI(4%), and
9. 37.5/2.5 dose vs 75/2.5 dose for ODI(4%).

All hypothesis tests will test that the two-sided p-value is less than 0.05.

All hypothesis tests for secondary endpoints will be reported using the nominal 0.05 two-sided alpha level.

## 4.6. Data Derivations and Transformations

Study Day will be calculated as:

- Date of assessment – date of randomization + 1 for assessments done on or after date of randomization
- Date of assessment – date of randomization for assessments done before date of randomization

For each efficacy and safety endpoint, the baseline value will be calculated as the last non-missing value prior to randomization (except where unscheduled assessments are performed the baseline value should be the value recorded at Screening). Where applicable, change from baseline values will be calculated as:

$$\text{Change from Baseline} = \text{assesment value} - \text{baseline value},$$

while the percent change from baseline values will be calculated as:

$$\text{percent change from baseline} = \frac{\text{change from baseline}}{\text{baseline value}} \times 100\%.$$

For the endpoints that look for the proportion of participants with ≥50% reduction, participants will be assigned a visit level indicator:

$$\text{Indicator of} \geq 50\% \text{ reduction} = \begin{cases} 1 & \text{if percent change from baseline} \leq -50\% \\ 0 & \text{otherwise} \end{cases}.$$

### 4.7. Modeling for Select Endpoints

In Section 6, modeling will be used for comparisons between study treatments with respect to given endpoints using the PROC GLIMMIX procedure in SAS. The model will include study treatment and visit as fixed effects. Within participant variability (nested within treatment sequence) will be modeled using an unstructured (e.g., TYPE = UN, CHOL) covariance pattern. The unstructured covariance parametrized through its Cholesky root is to be used for logistic regression models and models in which convergence fails for the completely unstructured covariance. Point (e.g., mean, difference of means) and inferential (e.g., confidence interval, p-values) statistics will provided be estimated using least squares (LS) methods. Unless otherwise stated, the link will be identity and the distribution gaussian.

## 5. STUDY PARTICIPANTS

### 5.1. Disposition of Participants

A table of frequency counts and percentages of all participants who are enrolled, distributed study medication, and included in each analysis set will be provided. Participant disposition including study completion status and reasons for early termination will be tabulated overall. A by-participant listing will be provided.

### 5.2. Protocol Deviations

Two separate by-participant listings for major and minor protocol deviations will be provided.

### 5.3. Demographic

Descriptive statistics will be used to summarize the demographic characteristics (age, gender, race, ethnicity, height, weight, and BMI) overall using the Safety Set. A by-participant listing will also be provided.

### 5.4. Baseline Characteristics

The results of the following assessments completed during the baseline PSG will be summarized overall using the Safety Set:

- AHI(4%)
- ODI(4%)
- HB(4%)
- Total time with $SaO_2$ <90%

- Snoring index
- Arousal indices (respiratory and spontaneous)
- Fraction of hypopneas
- WASO
- Sleep stage (N1, N2, N3, R) separately in minutes and percent of total sleep time
- Sleep efficiency
- Number of awakenings
- Sleep onset latency
- Heart rate
- Total sleep time
- Systolic blood pressure
- Diastolic blood pressure

The baseline PSG parameters and vital signs will be included in their respective general listings.

### 5.5. Medical History

All medical conditions and surgical procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. The number and percent of participants with each medical condition and surgical procedure will be presented by MedDRA system organ class (SOC), preferred term (PT) overall for the Safety Set. Each participant will be counted only once per SOC and PT. A by-participant listing will also be provided.

### 5.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using September 2020 B3 Global World Health Organization (WHO) Drug Dictionary version. The number and percent of participants using each medication will be tabulated by Anatomical Therapeutic Chemical (ATC) level 3, preferred name overall. Each prior or concomitant medication reported more than one time will only be counted once per participant for each ATC level and preferred name. A by-participant listing will also be provided.

## 6. EFFICACY ANALYSIS

The mITT Set will be used for all efficacy analyses.

### 6.1. Primary Efficacy Analysis – HB(4%)

Multiple comparisons will be performed as described in Section 4.5. A repeated measures model (see Section 4.7) will be used to model change in $\log_{10}$(HB[4%] + 1) from baseline. Model based LS mean estimates will be provided for the following:

- mean change by study treatment (75/2.5 dose, 37.5/2.5 dose, placebo),

- difference in mean change between study treatments[1] (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

If the model shows there is a visit (i.e., period) effect, then ad hoc analyses will be performed. A sensitivity analysis will be performed using the PP Set on the primary efficacy endpoint using the same methods described above and using HB(4%) with identity transform (i.e., without transform) on the mITT set.

Descriptive statistics for the reported value and change from baseline in $\log_{10}$(HB[4%] + 1) will be presented by study treatment. By taking the inverse transformations of the respective means, the geometric mean of HB(4%) + 1 and the ratio of the geometric mean to baseline will be reported.

## 6.2. Secondary Efficacy Analysis

### 6.2.1. HB(4%)

The secondary outcomes of 37.5/2.5 dose vs placebo and vs. 75/2.5 dose are described in the primary efficacy analysis for $\log_{10}$(HB[4%] + 1).

### 6.2.2. AHI(4%)

Multiple comparisons will be performed as described in Section 4.5. A repeated measures model (see Section 4.7) will be used to model change in AHI(4%) from baseline. Model based LS mean estimates will be provided for the following:

- mean change by study treatment (75/2.5 dose, 37.5/2.5 dose, placebo),
- difference in mean change between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

Descriptive statistics for the reported value and change from baseline in AHI(4%) will be presented by study treatment.

### 6.2.3. ODI(4%)

Multiple comparisons will be performed as described in Section 4.5. A repeated measures model (see Section 4.7) will be used to model change in ODI(4%) from baseline. Model based LS mean estimates will be provided for the following:

- mean change by study treatment (75/2.5 dose, 37.5/2.5 dose, placebo),
- difference in mean change between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

Descriptive statistics for the reported value and change from baseline in ODI(4%) will be presented by study treatment.

[1] Only 75/2.5 dose vs placebo is part of the primary outcome. The 37.5/2.5 dose vs placebo and 37.5/2.5 dose vs 75/2.5 dose are secondary outcomes.

### 6.2.4. Total time with SaO2<90%

Multiple comparisons will be performed as described in Section 4.5. A repeated measures model (see Section 4.7) will be used to model total time with SaO2<90%. Model based LS mean estimates will be provided for the following:

- mean change by study treatment (75/2.5 dose, 37.5/2.5 dose, placebo),
- difference in mean change between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

Descriptive statistics for the reported value and change from baseline in total time with SaO2<90% will be presented by study treatment.

### 6.2.5. Proportion of participants with ≥50% reduction

Three separate repeated measures models (see section 4.7) will be used to model the probability of a ≥50% reduction in AHI(4%), hypoxic burden, and ODI(4%) values respectively. A logit link with binomial distribution will be employed. For each of the three endpoints, model based LS mean estimates will be provided for the following:

- odds ratios for a ≥50% reduction between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

The proportion, with 95% CI, of participants with ≥50% reduction in AHI(4%), HB(4%), and ODI(4%) will be presented by study treatment in the same table as the models.

## 6.3. Tertiary Efficacy Analyses

### 6.3.1. KSS

Two separate repeated measure models (see section 4.7) will be used to model the probability of being alert (KSS score ≤3) and of not being sleepy (KSS score ≤5). A logit link with binomial distribution will be employed. For each of the two endpoints, model-based LS mean estimates will be provided for the following:

- odds ratios between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

Descriptive statistic of the proportion, with 95% CI, of participants alert and not sleepy will be presented by study treatment separately in the same table as the model. Number and percentages of participants with the individual score values (1-9) will be given by study treatment. A by-participant listing of the KSS scores will be given.

### 6.3.2. Sleep Quality VAS

A repeated measures model (see Section 4.7) will be used to model Sleep Quality VAS total score. Model based LS mean estimates will be provided for the following:

- mean score by study treatment (75/2.5 dose, 37.5/2.5 dose, placebo),

- difference in mean score between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with 95% confidence intervals and respective p-values (for null hypothesis).

Summary statistics of Sleep Quality VAS total score by study treatment and a by-participant listing will also be provided.

#### 6.3.3. PSG sleep and arousal parameters and alternate measures of AHI, ODI, and HB

Descriptive statistics for the reported value and change from baseline by study treatment will be reported for sleep stages distribution and percentage of time in the various sleep stages (SE, WASO, NAW, SOL, Stage N1%, Stage N2%, Stage N3%, Stage R%). A 95% confidence interval will be included for the change from baseline.

Snoring index, arousal indices (respiratory and spontaneous), fraction of hypopneas (see below) and alternate measures of AHI, ODI, and HB (AHI[4%]: in NREM sleep, in REM sleep, AHI adjusted for position [see below]; AHI[3% or arousal]; HB[3% or arousal]; HB[Total]; ODI[3%]) and will have results provided similar to Section 6.1 (including the model of change from baseline and the descriptive statistics).

Additional clarifying details for the analysis of some of these endpoints is as follows:

- Fraction of hypopneas will be calculated by using the number of hypopneas divided by the total number of apneas plus hypopneas.
- AHI adjusted for position: An additional covariate of % time supine (%TS) will be added to the repeated measures model for AHI(4%).

## 7. SAFETY ANALYSIS

Safety assessments will include measurement of adverse events (AEs) and serious AEs (SAEs).

The analyses will be descriptive and will be based on the Safety Set. The safety assessments will be summarized by the study treatment the participant actually received within each period.

### 7.1. Extent of Exposure

The number and percentage of participants receiving study treatment will be summarized by study treatment and overall. A by-patient listing will be provided.

### 7.2. Adverse Events

An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

#### 7.2.1. Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to exposure

of study drug or an event already present that worsens in either severity or frequency following exposure. Each TEAE is assigned to the most recent study treatment administered on or before the TEAE's date of onset.

### 7.2.2. Adverse Event Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

### 7.2.3. Adverse Event Relationship to Study Medication

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

### 7.2.4. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other situations.

### 7.2.5. Adverse Event Summaries

Adverse event data will be displayed in listings by participant. The number and percentage of participants with AEs will be tabulated by SOC and PT. A participant with multiple AEs within a SOC or PT will be counted once toward the total for the total for the SOC or PT.

All AEs (serious and non-serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and presented by MedDRA SOC and PT.

For TEAEs, the following will be summarized by study treatment and presented for the Safety Set.

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of participants experiencing any TEAE
   b. the number and percentage of participants experiencing any TEAE by strongest relationship to study medication
   c. the number and percentage of participants experiencing any TEAE by greatest intensity
   d. the number and percentage of participants experiencing any TESAE

ii. the number and percentage of participants experiencing any TEAE by SOC, PT

iii. the number and percentage of participants experiencing any TEAE by SOC, PT and the greatest intensity

iv. the number and percentage of participants experiencing any TEAE by SOC, PT and the strongest relationship to study medication

v. the number and percentage of participants experiencing any TEAE leading to study discontinuation by SOC and PT.

In the overall summary of AEs table, besides tabulating the number and percentage of participants, the total number of AE episodes will also be provided. If a participant has repeated episodes of a particular AE within a treatment period, all episodes will be counted in the summary table and displayed by treatment.

For displays by SOC and PT, each participant will be counted only once per SOC and PT within each treatment.

All occurrences of all AEs will be listed for each participant, grouped by treatment. The listing will contain the following information: treatment sequence, study treatment, SOC, PT, verbatim term, intensity, relationship to study medication, date and study day of onset, date and study day of resolution, treatment given to treat the adverse event, action taken, the outcome, whether the event was an SAE, whether it led to withdrawal. Listings will be sorted by treatment sequence, participant identification number, onset date, SOC, and PT. If onset year is non-missing but month and/or date is missing, then the day of the most recent study drug dose will be imputed as onset date.

### 7.3. Vital Signs

Vital sign data will be summarized by presenting descriptive statistics of actual values and changes from baseline by study treatment. Vital sign parameters include respiratory rate, temperature, systolic blood pressure, diastolic blood pressure, and heart rate. A by-participant listing of vital signs will also be provided.

### 7.4. Clinical laboratory values

Clinical laboratory values will be summarized by presenting descriptive statistics of actual values and changes from baseline for the end of study evaluation. Clinical laboratory values include urinalysis (dipstick and microscopic), hematology, and chemistry lab values. A by-participant listing of clinical laboratory values will also be provided.

### 7.5. DSST

A repeated measures model (see Section 4.7) will be used to model the natural log of total number of the correct symbol assignments[2] (log (total completed - total incorrect)) from the DSST.

Exponentiation of the model-based LS mean estimates of log values will be used to provide the following:

- Geometric mean of DSST by study treatment (75/2.5 dose, 37.5/2.5 dose, placebo), and
- Ratio of (geometric) mean of DSST between study treatments (75/2.5 dose vs placebo, 37.5/2.5 dose vs placebo, and 75/2.5 dose vs 37.5/2.5 dose) with the 95% confidence intervals.

Descriptive statistics of DSST and a by-participant listing (with both raw values and natural log of total complete) will also be provided.

### 7.6. PSG Parameters

PSG safety data will be summarized by presenting descriptive statistics of actual values and changes from baseline by study treatment. PSG safety parameters include total sleep time, heart rate, and total time with $SaO_2$<90%. A by-participant listing of PSG parameters (including baseline and efficacy parameters) will also be provided.

[2] In the case that the total correct is 0, the participant will be dropped from the model.

# 8. INTERIM ANALYSIS

No interim analysis is planned.

# 9. SAMPLE SIZE AND POWER CALCULATIONS

A total of 30 patients will enter the 3-treatment crossover study. The study will have 80% power to detect a treatment difference on the primary endpoint at a two-sided 0.05 significance level, if the true difference between treatments on HB is at least -3.7 % min/h. This assumes that the within-participant standard deviation is 9 and a discontinuation rate of less than 20%.

# 10. APPENDICES

## 10.1. Appendix A: Schedule of Activities

| Procedures | Screening | | 3-Way Crossover Period | | | | | | End of Study Evaluation |
|---|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | Wash-out [1] | V4 | Wash-out | V5 | Wash-out | |
| **Trial Day (Visit Window)** | **Up to 4 weeks** | | **Up to 6 weeks** | | | | | | **2 wks post V5 ± 3 d** |
| Informed consent | X | | | | | | | | |
| Non-PSG enrollment criteria[2] | X | | | | | | | | |
| Demography | X | | | | | | | | |
| Physical exam | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Clinical laboratory testing | X | | | | | | | | X |
| Pregnancy test[3] | X | | | | | | | | |
| 12 Lead ECG | X | | | | | | | | |
| PSG Exam | | X[4] | X | | X | | X | | |
| Randomization[5] | | | X | | | | | | |
| HS study treatment[6] | | | X | | X | | X | | |
| DSST, KSS, Sleep quality VAS[7] | | | X | | X | | X | | |
| Vital signs[8] | X | X | X | | X | | X | | |
| AE/SAE monitoring | | | X | X | X | X | X | X | X |
| Prior/concomitant medication | X | X | X | X | X | X | X | X | X |

[1] Each washout period is a minimum of 7 days
[2] Includes ESS, PGI-S, and history of OSA symptoms
[3] WOCBP only
[4] Only patients who meet all non-PSG enrollment criteria at Visit 1 are eligible for a screening PSG
[5] Randomization occurs when participant meets enrollment criteria up to the time of the first crossover period.
[6] Study medication administered immediately before lights out
[7] Administer at similar time after awakening after each crossover PSG, approximately 1 hour after awakening
[8] Vital signs include the following: seated blood pressure, pulse, respiratory rate; vital signs on PSG nights taken after admission to PSG lab.

## 10.2. Appendix B: Protocol-Required Safety Laboratory Assessments

| Laboratory Assessments | Parameters | | |
|---|---|---|---|
| Hematology | Hematocrit<br>Hemoglobin<br>Platelet Count<br>RBC Count | RBC Indices (MCV, MCH, MCHC) | WBC count with Differential |
| Serum Chemistry | Albumin<br>BUN<br>Creatinine<br>Potassium<br>Sodium<br>Bilirubin (total)<br>Total Protein<br>Uric acid | ALT<br>AST<br>Alkaline phosphatase<br>Calcium<br>Glucose<br>Total cholesterol<br>Chloride<br>Bicarbonate | |
| Routine Urinalysis | • Specific gravity, bilirubin, color, appearance, leukocyte esterase, nitrite, pH, protein (albumin), glucose, ketones, occult blood, urobilinogen<br>• Reflex microscopy | | |
| Other Tests | • HbA1c (Screening Visit only)<br>• Serum hCG pregnancy test at screening. Additional testing may be performed if needed in WOCBP.<br>• Urine test of drugs of abuse (marijuana, cocaine, amphetamine, methamphetamine, opiates, phencyclidine) | | |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HbA1c = hemoglobin A1c (glycated hemoglobin); hCG = human chorionic gonadotropin; RBC = red blood cell count; WBC= white blood cell; WOCBP = women of childbearing potential.

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