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November 3, 2022

To: ClinicalTrials.gov

This is a cover page to the redacted SAP for APN-002 titled Phase 2, Placebo-Controlled, Parallel Group Dose-Finding Study to Evaluate the Efficacy and Safety of Three Fixed-Dose Combinations of AD036 in Adults With Obstructive Sleep Apnea

The APN-002 SAP is associated with NCT 03845023.

The following proprietary information was redacted from the SAP for APN-002:

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

Sincerely,

DocuSigned by:
Jeanne Brittain
Signer Name: Jeanne Brittain
Signing Reason: I approve this document
Signing Time: 11/3/2022 | 1:00:42 PM EDT
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Jeanne Brittain
Director, Program Management

Quality Approval:			
Name	**Title**	**Signature**	**Date**
Francesca Kelvy	Senior Director, GXP Quality Assurance	DocuSigned by: Francesca Kelvy Signer Name: Francesca Kelvy Signing Reason: I approve this document Signing Time: 11/7/2022 | 9:16:45 AM EST 35E78DD6A7F34F8AA557BB15D08339BC	11/7/2022

16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Final Version 1.0, Dated 03 Oct 2019

PAREXEL International

Apnimed

APN-002 (240495)

Phase 2, Placebo-Controlled, Parallel Group Dose-Finding Study to Evaluate the Efficacy and Safety of Three Fixed-Dose Combinations of AD036 in Adults With Obstructive Sleep Apnea

Statistical Analysis Plan

Version: Final 1.0

PAREXEL Project Number: 240495

SPONSOR SIGNATURE PAGE

Approved by:

Ronald Farkas
Chief Medical Officer
Apnimed

3 Oct 2019
Date

PAREXEL SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

Signatory		Project Role
Author	Dave, Vimalkumar Digitally signed by Dave, Vimalkumar Date: 2019.10.03 23:44:55 +05'30' Vimalkumar Dave	Biostatistics Lead

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REVISION HISTORY

Version No.	Date	Author	Summary of Change(s)
1.0	03 Oct 2019	Vimalkumar Dave	New document

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AHI	Apnea-Hypopnea Index
AE	Adverse Event
ATO	Atomoxetine
ATO/OXY	Concurrent atomoxetine oxybutynin therapy
Bang	Body Mass Index, Age, Neck Circumference, And Gender Criteria
BMI	Body Mass Index
CNS	Central Nervous System
CSP	Clinical Study Protocol
CSSA	Cocaine Selective Severity Assessment
ECG	Electrocardiogram
EEG	Electroencephalogram
eCRF	Electronic Case Report Form(S)
EDC	Electronic Data Capture
EOS	End Of Study
ESS	Epworth Sleepiness Scale
ICF	Informed Consent Form
IPSS	International Prostate Symptom Score
MedDRA	Medical Dictionary for Regulatory Activities
OSA	Obstructive Sleep Apnea
OXY	Oxybutynin
PGI-S	Participant Global Impression Of Severity
PK	Pharmacokinetic(S)
PSG	Polysomnography
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SaO_2	Oxygen Saturation
SAP	Statistical Analysis Plan
SoA	Schedule Of Activities
STOP	Snoring, Tiredness, Observed Apnea, And Blood Pressure Criteria
SUSAR	Suspected Unexpected Serious Adverse Reaction

1 INTRODUCTION

The purpose of this Statistical Analysis Plan is to describe the planned analyses and reporting for Sponsor protocol APN-002 (240495), entitled "Phase 2, Placebo-Controlled, Parallel Group Dose-Finding Study to Evaluate the Efficacy and Safety of Three Fixed-Dose Combinations of AD036 in Adults with Obstructive Sleep Apnea.

This Phase 2B clinical study is designed to examine the efficacy and safety of AD036 (combination of atomoxetine and oxybutynin) at concentrations that are both similar to the concentration used in the first in human study, and at 2 lower doses, versus placebo. Overall, the study is expected to provide dose selection guidance and a deeper understanding of repeat-dose safety and tolerability for the ongoing clinical development of AD036.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 1.4 (Dec 04, 2018)
- Electronic Case Report Form (eCRF), Version 1.0 (Jan 31, 2019)

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonized Tripartite Guideline Statistical Principles for Clinical Trials E9 [1]

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP Addendum. In this SAP, terminologies like Subjects, Participant or Patients means participants enrolled in the study.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

1. To assess the efficacy of 3 different fixed doses of AD036 (the combination of atomoxetine and oxybutynin) vs. placebo.
2. To evaluate safety and tolerability of the combination AD036.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase 2, randomized, double blind, placebo-controlled, repeat-dose, parallel arm, outpatient and inpatient, multi-center, dose finding study of the combination of atomoxetine and oxybutynin in adults with obstructive sleep apnea (OSA) documented by polysomnography (PSG).

Number of Participants and Randomization: Approximately 140 participants will be randomized to study treatment in equal ratio (1:1:1:1), at least 35 participants per arm, to 1 of 4 parallel treatment groups. At a study site, multiple randomizations may occur within a single arm in a short period of time, temporarily leaving no investigational product available for the given study arm while resupply is sent from the depot. Consequently, if a subsequent randomization is to the same study arm, that randomization number will be skipped, and the patient will be randomly allocated to the next free number in the randomization list corresponding to one of the treatments in stock at the site, i.e. "forced randomization". Skipped randomization numbers will remain unallocated.

Treatment Groups and Duration: There will be 4 parallel treatment groups, as follows:

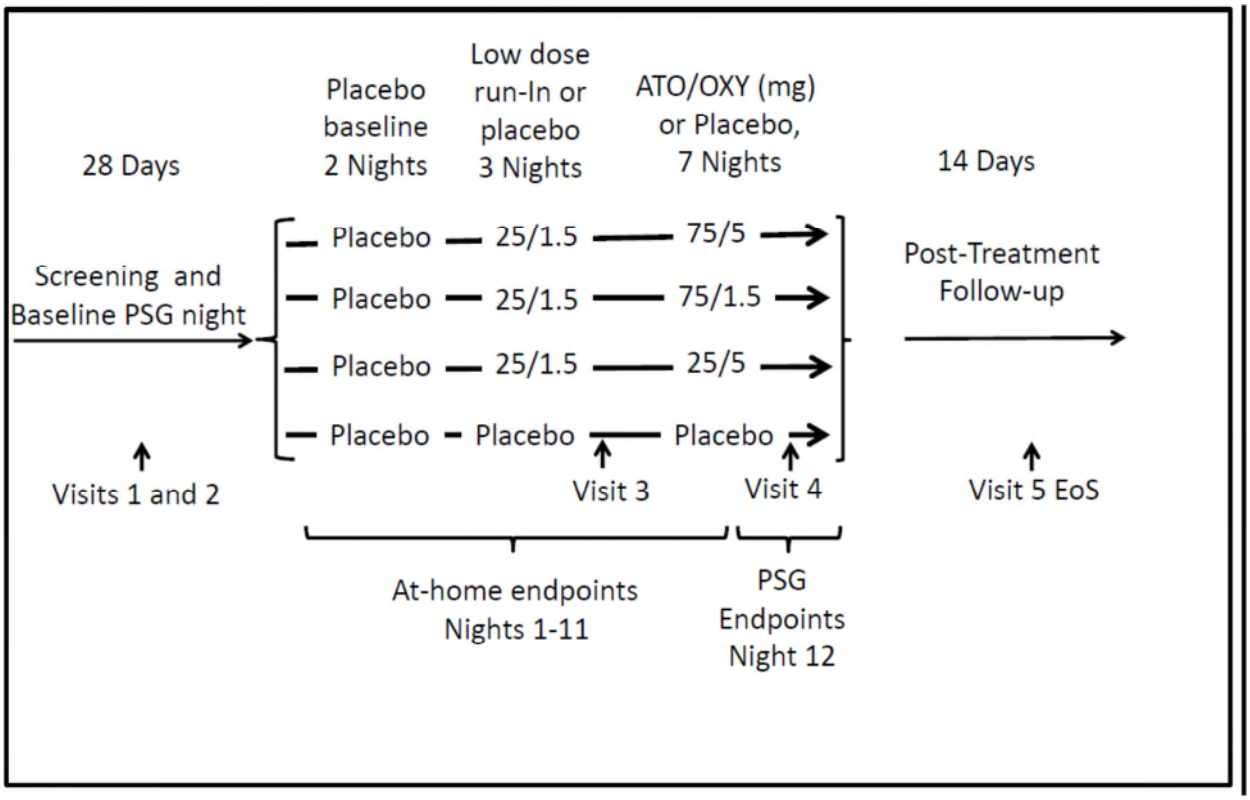
Group	Atomoxetine/oxybutynin (mg)	Subjects (n)
1	75/5	35
2	75/1.5	35
3	25/5	35
4	Placebo	35

Overall study duration will be up to 8-9 weeks, with up to 28 days for screening and baseline PSG. All participants will receive placebo for 2 days to establish baseline measures. Participants assigned to active treatment will subsequently receive low dose (25 mg atomoxetine/1.5 mg oxybutynin) for a 3-day dose-escalation period. Participants randomized to placebo will have a placebo run-in period.

Following the dose-escalation period, participants will receive the dose level to which they were randomized (75/5; 75/1.5; 25/5; placebo) for 7 (±2) nights (6 nights at home, seventh night inpatient PSG). On the final night of dosing, participants will return for inpatient PSG (Visit 4). A follow-up safety visit will take place 2 weeks post study treatment dosing (±2 days), or upon early withdrawal (figure 1).

Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Figure 1 – Overall Study design



Abbreviations: ATO = atomoxetine; EoS = end of study; OXY = oxybutynin; PSG = polysomnography

3.2 Endpoints and Associated Variables

3.2.1 Primary Efficacy Endpoint

Comparison of the proportion of participants with ⩾50% reduction in apnea-hypopnea index (AHI) from baseline to the second PSG visit in the atomoxetine 75 mg/oxybutynin 5 mg dose group compared with placebo.

3.2.2 Primary Safety & Functional Endpoints

Safety Endpoints

1. The number and percentage of participants reporting Adverse Events (AEs), including the post-dosing period
2. Change from baseline in physical examination findings
3. Change from baseline in clinical laboratory testing (hematology, serum chemistry, urinalysis, other tests)
4. Cocaine Selective Severity Assessment (CSSA) results, Modified for study treatment
5. Prospective Suicidality Assessment (item 17 “suicidality” of CSSA) results

6. Change from baseline in PSG parameters: heart rate, electrocardiogram (ECG), electroencephalogram (EEG), oximetry
7. Change from baseline in vital signs, ECG

Functional Endpoints

1. Digit Symbol Substitution Test (DSST) results
2. Delayed Word Recall Test (DWRT) results

3.2.3 Secondary Efficacy Endpoints

1. Percent change AHI, high-dose arm (atomoxetine 75 mg/oxybutynin 5 mg dose) vs. placebo.
2. Proportion of participants with ≥50% reduction in AHI, measured in the supine sleeping position, from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
3. Proportion of participants with ≥50% reduction in Oxygen desaturation index from baseline (average of 2 baseline nights) to study treatment nights (average of 6 nights) for the 75/5 dose group compared with placebo.
4. Change from baseline in the Epworth Sleepiness Scale (ESS) from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
5. Change from baseline in the Participant Global Impression of Severity (PGI-S) from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
6. Proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit in the 75/5 dose group compared with the lower treatment dose of 25/5.
7. In the case that a statistically significant result for the AHI comparison of dose 75/5 to 25/5 is observed, then the proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit in the 75/5 dose group compared with the lower treatment dose of 75/1.5.

3.2.4 Tertiary/Exploratory Endpoints

1. Proportion of participants with ≥50% AHI decrease and final AHI<15/hour, PSG nights
2. Total time with oxygen saturation (SaO_2) <90%, PSG nights
3. Total time with SaO_2 <80%, PSG nights
4. Snoring index, PSG nights

5. Sleep stages distribution and % of time in the various sleep stages, PSG nights
6. Arousal index, PSG nights
7. Oxygen desaturation index, low-dose run in vs baseline, at home nights
8. Proportion of apneas to hypopneas
9. Proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit
10. Correlation of phenotypic traits (Vpassive, Vactive, arousal threshold and Loop gain) with AHI response or subjective outcomes

3.2.5 Safety Variables

3.2.5.1 Adverse event

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.

AEs will be collected from the signing of the informed consent form (ICF) to the follow-up visit (Visit 5/End of study). Each AE verbatim term will be coded to a system organ class and a preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

For patient level summaries, if more than one AE is coded to the same PT for the same patient, the patient will be counted only once in summary tables using the most serious grading on causal relationship to study treatment.

3.2.5.2 Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

3.2.5.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSAR is defined as an AE that is serious, associated with the use of the study treatment, and unexpected and has additional reporting requirements, as described in section 10.3 of the Clinical Study Protocol (CSP).

3.2.5.4 Clinical laboratory testing

Laboratory data will be collected throughout the study, from screening to the follow-up visit as per the study plan described in the CSP. Hematology, serum chemistry, urinalysis, and others as clinically indicated will be collected as described in section 10.2 of the CSP.

Missing laboratory data will not be imputed. However, laboratory assessment values of the form of "<x" (i.e., below the lower limit of quantification) or >x (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

3.2.5.5 Cocaine Selective Severity Assessment (CSSA)

A modified version of the CSSA will be used to measure potential withdrawal signs and symptoms from the study treatment; "cocaine" will be replaced with "study drug". The CSSA includes psychiatric symptoms of general safety interest such as changes in sleep, anxiety, energy level, activity level, tension, attention, paranoid ideation, anhedonia, depression, suicidality, and irritability. Items are rated on a scale of 0-7, and a total score is derived by summing the individual items.

3.2.5.6 Prospective Suicidality Assessment

The CSSA item 17, "suicidality", will be used to monitor participants for suicidality during the study (whether or not abuse-related). A score of ⩾3 will be considered an AE.

3.2.5.7 Pregnancy records

Details of all pregnancies in female participants and female partners of male participants after the start of study treatment and until at least 5 terminal half-lives after the last dose will be collected. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures. The data extraction will be set to appropriate date so that all data cleaning activities at site are taken care of.

4.2 Study Subjects

4.2.1 Disposition of Subjects

A clear accounting of the disposition of all enrolled subjects who enter the study will be provided, from screening to study completion.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered into the study.
Summaries of subject disposition will be presented by treatment and overall.

The following patient disposition summaries will be provided

- A summary of the number and percentage of subjects who were screened, screen failure, randomized, randomized but were not treated (not a single dose of the study treatment) will be provided. This summary will be based on total screened subjects.
- A separate summary table for subjects who completed, discontinued and the primary reason(s) for discontinuation will be provided for each treatment group. This summary will be based on mITT Population.
- Subject disposition including the subject status (completer, Yes/No), demographic data (age and race), screening date, study product start date and time, the duration in the study or trial, date of discontinuation and the specific reason for discontinuation, will be listed for randomized subjects by product group and center.

4.2.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to un-blinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with major protocol deviations (defined below) will be excluded from the PP population.

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for primary analysis. This will include all those deviations to be reported in the clinical study report (CSR).

The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 4.4), both including and excluding data potentially affected by major protocol deviations. The final determination of major protocol deviations and the exclusion of patients from each of the analysis populations will be made prior to database lock. Please refer to the study protocol deviation specification for more information.

In the event that a subject is allocated the incorrect study treatment as per the study randomization list, it will be considered as a protocol deviation.

The number of subjects with protocol deviations will be summarized by category (Major or Minor) and deviation classification overall and by treatment group. Protocol deviations will be listed with date and study day of occurrence, deviation category, deviation description and analysis populations from which subject is excluded.

The number of subjects included in each analysis population will be summarized. A listing of subjects included in each analysis population will also be provided. Subject exclusion from analysis sets will be listed with reasons for exclusions.

Blinding of the study will be maintained as per the Blinding Maintenance Plan which has been developed and approved on 13March2019.

4.3 Analysis Sets

Enrolled Population

All participants who signed the ICF (including screening failures).

Modified Intent to Treat (mITT) Population

The efficacy summaries and analyses will be based on the mITT Population**,** which is based upon the Intention-to-Treat principle. The mITT Population 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. The mITT population will therefore include patients who have a primary endpoint measurement at either Visit 2 (baseline) or Visit 4 (on treatment), or both. Participants will be analyzed for efficacy according to the treatment group into which they are randomized.

If a subject is allocated the incorrect study treatment as per the study randomization list, subjects will be summarized and analyzed 'as randomized' i.e. by randomized treatment group.

Safety Population

The safety summaries and analyses will be based on the Safety Population. The Safety Population consists of all participants who are randomized and receive at least 1 dose of any of the study treatments. Participants will be analyzed "as actually received" (i.e., according to the actual treatment received during randomization).

Per Protocol (PP) Population

The PP Population consists of all participants without any major protocol violations that could influence efficacy assessment, and who are at least 80% compliant with the study medication. Participants in this population will be analyzed according to the treatment they actually received.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to Apnimed for review. An analysis population classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented and approved by Apnimed.

Sensitivity analyses will be performed on the PP population for key primary and key secondary efficacy endpoints (key comparisons for which sequential order is specified, please refer section 9.4 of the protocol or 4.9.1.4 of the SAP) to understand the impact of

major protocol deviations on study results. Sensitivity analyses will separately be performed on the PP population excluding patients whose randomization was “forced”.

4.4 Demographics and Baseline Characteristics

Descriptive statistics (number of subjects [n], mean, median, standard deviation [SD], minimum and maximum) for the continuous variables and frequency (n) and percentages (%) for categorical variables will be provided for demographic variables.

The continuous variable includes age (years) height (Meter), weight (kg), BMI,

International Prostate Symptom Score (IPSS), AHI Score and categorical variables include gender, race, and Ethnicity, STOP BANG Score (5-8 [High risk of OSA], 3-4 [Intermediate OSA], 0-2[Low Risk]).

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent. If age is missing but date of birth is present, age will be calculated as follows (without rounding):

Age (years) = (study day 1 – date of birth) / 365.25

This will be determined from the date of birth (birth date in the Demographics eCRF page) and baseline visit (‘visit 1’ in the Date of visit eCRF page). If the day of birth is missing, the first day of the month will be imputed and if day and month are missing January 1st will be imputed.

4.5 General Presentation Considerations

All statistical analyses will be performed using SAS® software Version 9.3 or later.

Medical history and AEs will be coded using the latest version of MedDRA. The frequency count and percentage of subjects will be summarized according to the coded terms of system organ class (SOC) and preferred term (PT). Subject-wise data listing will be provided.

For participants who are eligible and enroll in the study, the screening PSG night will serve as the baseline measure for AHI and other PSG efficacy and safety endpoints. Baseline measures for additional secondary and tertiary endpoints based on home oximetry will be recorded at home during the placebo period, and these endpoint measures will continue to be collected over the subsequent at-home study treatment dosing period. On the final night of dosing (Visit 4), participants will return for inpatient PSG.

A participant is considered to have completed the study if he/she has completed all phases including Screening (visit 1), Baseline (visit 2), placebo baseline (2 night (Day 1-2), low dose run-in or placebo night (3 night [Day 3-5 +2]), ATO/OXY (mg) or placebo 7 night (Day 6-12 +/- 2) and the final Follow-up visit or the last scheduled procedure shown in the Schedule of Activities (SoA) (Appendix).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will be presented for zero counts along with 95%confidence interval (CI) where applicable. Percentages will be calculated using 'n' (the total number of subjects providing data at the relevant time point) as the denominator. Percentages will not be presented for zero counts. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

In all summaries change from baseline variables will be calculated as

Change from baseline = post-treatment value - baseline value.

The percentage change from baseline will be calculated as

Percent change from baseline = [(post-baseline value - baseline value) / baseline value] ×100.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Change from baseline and percent change from baseline will be calculated if both baseline and post-baseline data is available.

Confidence intervals will be presented to one more decimal place than the respective point estimator.

4.6 Medical History and Concomitant Therapy

Relevant medical history (past and current) and relevant surgical history will be coded using the latest version of MedDRA.

Concomitant procedures will be coded using the latest version of MedDRA, and will be summarized for the safety population by SOC and PT.

Moreover, the prohibited or restricted concomitant therapies (see section 6.5 of the CSP) will be summarized.

4.7 Prior and Concomitant Medications

The World Health Organization (WHO) Drug dictionary will be used for concomitant medication coding.

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

4.8 Treatment Exposure / Compliance

4.8.1 Treatment Exposure

Exposure to study treatment will be summarized by treatment group for the safety population by durations of drug exposure (days), total number of capsules received, and total number of capsules dispensed. Doses that were not given because the patient discontinued will not be summarized.

4.8.2 Compliance

Treatment compliance is calculated as the proportion in percentage of the scheduled expected number of doses, i.e. (Actual exposure/Expected exposure) *100.

A table with proportion of subjects with compliance and Non-compliance (Subject would be considered non-compliant if the subject consumes less than 80% of the total amount of recommended dose.) will be presented. Non-compliance will be assessed on a subject by subject basis. Those subjects with treatment compliance less than 80% will be excluded from the PP analysis. Any subject excluded from PP analysis will be clearly documented. Treatment compliance listing will be presented

4.9 Efficacy Evaluation

4.9.1 Analysis and Data Conventions

The high-dose AD036 in this study is atomoxetine 75 mg/ oxybutynin 5 mg, similar to the dose used in initial human studies (atomoxetine 80 mg/oxybutynin 5 mg). To explore the potential efficacy and safety of lower atomoxetine and oxybutynin doses, the following 2 additional dose arms will be studied: atomoxetine 75 mg/oxybutynin 1.5 mg and atomoxetine 25 mg/oxybutynin 5 mg. This Phase 2 clinical study will further examine the efficacy and safety of lower dose AD036 versus placebo.

The primary objective (s) of this study is to assess the efficacy of 3 different fixed doses of AD036 (the combination of atomoxetine and oxybutynin) vs. placebo.

The primary endpoint is the proportion of participants with ⩾50% reduction in AHI from baseline to the second PSG visit (Visit 4).

The primary comparison of the study is

- ATO 75 mg/OXY 5 mg vs placebo in the proportion of participants with ⩾50% reduction in AHI from baseline to the second PSG visit (Visit 4).

Primary null hypothesis will be

H0: Odds ratio for ATO 75 mg/OXY 5 mg versus placebo in participants with ≥50% reduction in AHI from baseline to the second PSG visit (Visit 4) = 1

Primary alternative hypothesis will be

H1: Odds ratio for ATO 75 mg/OXY 5 mg versus placebo in participants with ≥50% reduction in AHI from baseline to the second PSG visit (Visit 4) ≠ 1.

The other efficacy comparisons of interest also will be tested using logistic regression similar to primary efficacy hypothesis.

Participants that discontinue prior to the second PSG visit will not be replaced and will be considered non-responders.

When change from baseline is assessed at a post-baseline visit, unless otherwise specified, only patients with both baseline and post-baseline measurements will be included in the analyses. If baseline or post-baseline value is missing for a patient, then the change from baseline will be set to missing.

For all PSG safety and efficacy endpoints the screening PSG night (Visit 2) will serve as the baseline. For additional secondary and tertiary endpoints based on home oximetry, the average of the two baseline nights (Placebo baseline two night) will serve as the baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

For all efficacy endpoints, descriptive summary statistics for absolute values, change or percent change from baseline, if applicable, will be provided by analysis visits for mITT population and PP population.
For primary and key secondary endpoint analysis based on logistic regression odds ratio and 95% Wald confidence limits will be presented.

For primary and all key secondary endpoint line graph or bar graph will be created and details will be provided in the TLFs shell document.

4.9.1.1 Multi-center Studies

For the summaries and analyses purpose, the term 'Center' will be used to define each investigator site.

4.9.1.2 Adjustments for Covariates

Baseline values for all endpoint will be included as a covariate for all efficacy analysis.

4.9.1.3 Handling of Dropouts or Missing Data

Participants that discontinue prior to the second PSG visit will not be replaced and will be considered non-responders (<50% improvement in the AHI score).

Subject with missing baseline data will also be consider as the non-responder.

Responder are defined as the participant who shows ≥ 50% improvement in the AHI Score.

For all other endpoint missing data will not be imputed.

4.9.1.4 Multiple Comparisons/Multiplicity

Hypothesis tests will be performed in a sequential manner to avoid the need to adjust type I error rates for multiplicity, at a 2-sided 0.05 significance level. The sequential order of hypothesis tests will occur as follows:

- Comparison of the proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
- Percent change AHI, high-dose arm vs. placebo.
- Proportion of participants with ≥50% improvement in AHI, measured in the supine sleeping position, from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
- Proportion of participants with ≥50% improvement in Oxygen desaturation index from baseline (average of 2 baseline nights) to study treatment nights (average of 6 nights) for the 75/5 dose group compared with placebo.
- Change from baseline in the Epworth Sleepiness Scale (ESS) from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
- Change from baseline in the Participant Global Impression of Severity (PGI-S) from baseline to the second PSG visit in the 75/5 dose group compared with placebo.

- Proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit in the 75/5 dose group compared with the lower treatment dose of 25/5.
- In the case that a statistically significant result for the AHI comparison of dose 75/5 to 25/5 is observed, then the proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit in the 75/5 dose group will be compared with the lower treatment dose of 75/1.5.

4.9.1.5 Interim Analyses

No formal interim analysis is planned.

4.9.1.6 Examination of Subgroups

As a part of the additional exploratory analysis the uniformity of the treatment effect for the primary efficacy variable will be examined for the following subgroups:

1. Subgroup 1 – Baseline AHI Score ≤30 and BMI <35,
2. Subgroup 2 - Baseline AHI Score >30 or BMI ≥35

The homogeneity of the treatment effect across subgroups will be investigated. In addition, a statistical test for the presence of a treatment-by-subgroup interaction will be performed, by including the interaction term in the primary analysis model. The treatment-by-subgroup interaction will be investigated at 10% level ($p<0.10$).

Summaries of the primary efficacy variable by treatment group and subgroup will be produced. No formal statistical analysis will be performed within subgroup.

4.9.2 Primary Efficacy Variable(s)

Primary efficacy variable is participants with ≥50% improvement in AHI score from baseline.

Primary efficacy variable will be summarized by treatment group and visit.

Summaries will include the total number of subjects with assessments, the number of participants with missing measurements, proportion of subjects with ⩾50% improvement in AHI from baseline and associated 95% confidence intervals.

The primary efficacy endpoint will be analyzed using a logistic regression model with the treatment group as factor and baseline AHI score as a covariate. Estimate of the odds ratio along with associated 95% Wald confidence interval (CI) and two-sided p-value will be presented for primary comparison between 75 mg/5mg dose group and placebo.

Odds ratio estimates, CIs, and p-values will also be presented for other efficacy comparisons under the primary objective:

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm

4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

In the situation of zero events (or < 5 participants) in treatment groups, the logistic model may fail to provide valid parameter estimates. In this situation exact logistic regression (Fisher's exact test) can be used to compare the proportions across treatment groups.

A by-subject listing of the primary efficacy data will be provided.

The primary endpoint analysis will be based on mITT and PP population.

4.9.3 Secondary Efficacy Variables

To control the type I error, a sequential testing procedure will be employed with the order of hypothesis defined as in Section 3.2.2 above. All comparisons will be carried out and their result will be interpreted carefully.

Percent change AHI, high-dose arm vs. placebo.

Percent change AHI will be compared between high-dose arm and placebo group using an analysis of covariance (ANCOVA) model with treatment group as factor and baseline AHI (Visit 2) as a covariate. In the ANCOVA model.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for the following treatment comparisons on the percent change AHI score at two-sided 0.05 level of significance.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Proportion of participants with ≥50% improvement in AHI, measured in the supine sleeping position, from baseline (Visit 2) to the second PSG visit (Visit 4) in the 75/5 dose group compared with placebo.

Proportion of patients with ≥50% improvement in AHI, measured in the supine sleeping position, from baseline to the second PSG visit between 75/5 dose and placebo group will be analyzed using a logistic regression model with the treatment group as factors and baseline AHI Score as a covariate.

Estimate of the odds ratio along with associated 95% Wald confidence interval (CI) and two-sided p-value will be presented

Similar analysis will be carried out for the following treatment comparison on this efficacy variable at two-sided 0.05 level of significance.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Proportion of participants with ⩾50% improvement in at-home Oxygen desaturation index from baseline (average of 2 baseline nights) to study treatment nights (average of 6 nights) for the 75/5 dose group compared with placebo.

The oxygen desaturation index is the average number of oxygen desaturations 4% or more below the baseline level per hour.

Proportion of patients with ≥50% improvement in Oxygen desaturation index from baseline to study treatment nights (average of 6 nights) between 75/5 dose and placebo group will be analyzed using a logistic regression model with the treatment group as factors and baseline Oxygen desaturation index as a covariate.

Estimate of the odds ratio along with associated 95% Wald confidence interval (CI) and two-sided p-value will be presented

Similar analysis will be carried out for the each of following treatment comparison on this efficacy variable

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Change in the ESS from baseline to the second PSG visit in the 75/5 dose group compared with placebo.

Change from baseline in the ESS at second PSG visit (visit 4) will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for the each of following treatment comparison on this efficacy variable.

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Change in the PGI-S from baseline to the second PSG visit in the 75/5 dose group compared with placebo.

Change from baseline in the PGI-S at second PSG visit (visit 4) will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.
Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for the each of following treatment comparison on this efficacy variable.
All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

4.9.4 Tertiary/Exploratory Variables

Proportion of participants with ≥50% AHI decrease and final AHI<15/hour, PSG nights

Proportion of patients with ≥50% AHI decrease and final AHI<15/hour between baseline at Visit 4 will be analyzed using a logistic regression model with the treatment group as factors and baseline AHI score as a covariate.

Estimate of the odds ratio along with associated 95% Wald confidence interval (CI) and two-sided p-value will be presented

Similar analysis will be carried out for following treatment comparison

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Total sleep time with SaO_2 <90%, PSG nights

A summary of the number and percentage of subjects who had total sleep time (minutes) with SaO_2 <90% during PSG nights will be provided for each treatment group.

Change from baseline in the total sleep time with SaO_2<90 % at second PSG visit (visit 4) will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for following treatment comparison

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Total sleep time with SaO_2 <80%, PSG nights

Similar analysis will be performed for this endpoint as specified for the endpoint "*Total sleep time with SaO_2 <90%, PSG nights*"

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Snoring index, PSG nights

Snoring index is defined as number of snores per hour of sleep.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline of snoring index will be presented by study visits and treatment group.

Change from baseline in the Snoring index at second PSG visit (visit 4) will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence

interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for following treatment comparison

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Percent of sleep time in the various sleep stages, PSG nights

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline of percent sleep time in each sleep stages (WASO, Stage N1, Stage N2, Stage N3, Stage REM) will be provided by study visits and treatment group. The percentage of time in each sleep stage will be calculated using two different denominators; 1) amount of time the patient was asleep, 2) total recording time.

Arousal index, PSG nights

Arousal is defined as the total number of all arousals per hour of sleep.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline of arousal index will be presented by treatment group.

Change from baseline in the Arousal index at second PSG visit (visit 4) will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for following treatment comparison

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Oxygen desaturation index, low-dose run in (25/1.5) vs. placebo, or vs 75/5 final dose, at-home nights

The oxygen desaturation index is the average number of oxygen desaturations 4% or more below the baseline level per hour of sleep.

Proportion of patients with ≥50% improvement in Oxygen desaturation index will be presented for the following comparisons:

1. Within the 75/5 dose arm, proportion of ODI responders in 75/5 dose period vs proportion of ODI responders 25/1.5 low dose run-in period. The responders in 75/5 dose period will be calculated from average of 2 baseline nights to average of 6 treatment nights and the responders in 25/1.5 dose period will be calculated from average of 2 baseline nights to average of 3 run-in nights.
2. For all 3 active arms combined (i.e. 75/5;75/1.5;25/5) proportion of ODI responders in 25/1.5 low dose run-in period vs proportion of ODI responders in placebo period. The responders will be calculated from average of 2 baseline nights to average of 3 run-in nights and then the comparison will be done between combined active treatments vs placebo.

Estimate of the odds ratio along with associated 95% Wald confidence interval (CI) and two-sided p-value will be presented

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

Proportion of apneas to hypopneas

Proportion of apneas to hypopneas is defined as = H/(A+H).

Where,

A-Number of Apnea with onset during TST

H-Number of Hypopnea with onset during TST

This variable will be derived for each individual subject at both PSG visit (Visit 2 and Visit 4)

Change from baseline in the proportion of apneas to hypopneas at second PSG visit (visit 4) will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

Similar analysis will be carried out for following treatment comparison on this efficacy variable.

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

Correlation of phenotypic traits (Vpassive, Vactive, arousal threshold and Loop gain) with AHI response or subjective outcomes

Sponsor's research team and scientific advisors will perform this exploratory analysis using the PSG data to quantify two key contributors to OSA—pharyngeal collapsibility and compensatory muscle responsiveness—that is applicable to diagnostic polysomnography.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the safety population as defined in Section 4.4.

4.10.1 Adverse Events

AEs will be coded using MedDRA. The final version used will be designated in the clinical study report. For each AE, the severity level of the event (mild, moderate, or severe) will be determined by Investigator opinion.

Summary information including the number and percentage of subjects for treatment and overall by SOC and PT will be tabulated for:

- All AEs
- Pre-Treatment AE
- All AEs causally related (Related or Possibly related) to study treatment (as determined by the reporting investigator e.g. Not Related, unlikely related, possibly related, related)
- All SAEs
- All SAEs causally related (Related or Possibly related) to study treatment (as determined by the reporting investigator)
- All SUSARs
- All TEAEs
- All TEAEs causally related (Related or Possibly related) to study treatment (as determined by the reporting investigator)
- AEs that lead to discontinuation of study treatment
- All adverse events of special interest (AESI)
- TEAEs leading to death
- AEs by severity
- TEAEs by severity

A Pre-treatment AE will be defined as any AE with an onset date before the date of first administration of study treatment.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC.

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed.

A by-subject listing of all adverse events will be provided. This listing will be presented by treatment group and will include: center, subject identifier, age, sex, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome and causality.

A summary of the number of subjects with TEAE outcome into "Not recovered/Not resolved", "Recovered/Resolved", "Recovered/Resolved with sequelae", "Recovering/Resolving", "Fatal", and "Unknown" categories for number of events by treatment group and overall will be provided.

Death will be summarized by cause of death by the number and percentage of subjects experiencing events by treatment group and overall. Death data will also be listed.
Patients who experienced a SAE will be listed.

Imputation of partial dates

AE start date

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st.
- If year and month are present and day is missing, impute day as first day of the month.

AE end date

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31st.
- If year and month are present and day is missing, impute day as last day of the month.
- When the patient has died in the same month/year of partial stop date, use date of death.

In addition, for AEs, if for a partial start date, the AE start date could (when also considering the AE end date) potentially be on the first dose of study treatment date, the AE start date will be imputed with the first dose of study treatment date to assume a "worst case" scenario; e.g. AE from UNK-Jun-2017 to 23-Jul-2017 with the first dose of study treatment date 21-Jun-2017, then the AE start date will be imputed to 21-Jun-2017.

4.10.2 Clinical Laboratory Evaluation

An absolute value change from baseline and percentage change from baseline for all continuous hematology, serum chemistry and urinalysis laboratory parameter will be

summarized by analysis visit and treatment group, including scheduled and unscheduled assessment on-study period which spans the time drug is administered until the day of the patient's last contact date within the study, will be provided.

All laboratory test results will be listed by subject and study time point including changes from baseline (with the exception of urinalysis).

A separate listing will contain only values outside of normal ranges.

The number and percent of patients with clinically relevant abnormal laboratory findings will be tabulated by treatment group. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

Shift tables from baseline for the following category will also be provided.

- Hematology: Hemoglobin, Platelet Count, RBC Count, White Cells Count
- Serum chemistry: Albumin, ALT, AST, Creatinine, Alkaline phosphatase, Potassium, Calcium, Sodium, Bilirubin, Total cholesterol, Glucose, Protein, Uric acid, Bicarbonate

For all other lab tests listing will be provided.

4.10.3 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

The following vital signs measurements will be obtained:

- Systolic blood pressure (SBP) [mmHg].
- Diastolic blood pressure (DBP) [mmHg].
- Pulse rate (bpm).
- Body temperature (oral) [°C].
- Respiratory rate.

Vital signs data will be listed by subject including changes from baseline. The baseline for the vital signs measurements will be the measurement at screening.

Absolute values and changes from baseline will be presented by study visit and treatment group.

Participants who experience systolic blood pressure $\geqslant$ 160, or diastolic blood pressure $\geqslant$ 100, or heart rate $\geqslant$ 120 beats per minute will be tabulated separately. If triplicate vital signs are taken at a time point, the average value of the three measurements will be used for the above cutoffs.

Shift tables from baseline for the following category will also be provided.

- Systolic blood pressure (SBP) [mmHg].

- Diastolic blood pressure (DBP) [mmHg].
- Pulse rate (bpm).

12-Lead ECG

The following ECG parameters will be recorded:

- PR-interval (msec).
- QRS-interval (msec).
- QT-interval (msec).
- QTcF-interval (msec).
- Heart rate (HR) (beats per minute [bpm]).

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

All ECG parameters will be listed by subject for each study visit and treatment group including changes from baseline. The baseline for the ECG measurements will be obtained at screening.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by study visit and treatment group.

A categorical summary for change from baseline for QT and QTcF interval (msec) will also be provided.

Physical Examination

Physical examination findings will be summarized by body system for each treatment group at screening/baseline.

All individual physical examination findings will be listed.

Pregnancy test

Positive pregnancy test results will be listed only.

4.10.4 CSSA

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented for each CSSA item and the total score by treatment group at visit 4, visit 5 and if data is available Post 1 week of EOS. Only absolute values will be presented for Questions 4 and 5.

All individual CSSA data will be listed as well.

4.10.5 Prospective Suicidality Assessment

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by study visit and treatment group.

A summary of number and percentage of subjects with a score of <3 and ≥ 3 on prospective suicidality assessment will be displayed in a frequency table by study visit and treatment group.

A listing of patients by treatment arm with a shift of score from <3 to ≥3 on prospective suicidality assessment will be displayed.

4.10.6 Safety Monitoring

Safety monitoring will be guided by the established safety profiles of atomoxetine and oxybutynin, and by Phase 1 safety data for the combination. Safety assessments will include physical examinations, measurement of vital signs, monitoring and recording of AEs, SAEs, and pregnancies, suicidality assessment, recording of study or treatment discontinuations, measurement of ECGs, clinical laboratory evaluations, and memory testing. Effects on OSA and sleep parameters (e.g., sleep time and sleep stages) will also be monitored by PSG.

Adverse events of special interest include effects on urine outflow, as both atomoxetine and oxybutynin are associated with urinary retention. Effects of atomoxetine on heart rate and blood pressure are expected to be modest and will also be monitored. Participants with serious cardiac abnormalities will be excluded from the study. Suicidal ideation in children and adolescents is a boxed warning for atomoxetine; however, analysis in adult patients, the target population for the proposed OSA study, did not reveal an increased risk of suicidal ideation or behavior in association with atomoxetine. Safety monitoring in the dose-finding study will use an appropriate questionnaire to monitor for the potential emergence of suicidal ideation or behavior.

Daytime sleepiness is both a potential safety outcome and efficacy outcome in OSA. Both atomoxetine and oxybutynin are associated with somnolence, and oxybutynin is additionally associated with anticholinergic central nervous system (CNS) effects such as memory difficulty. Safety monitoring will therefore include psychomotor vigilance testing and memory testing.

4.11 Other Analyses

4.11.1 Digit Symbol Substitution Test (DSST) Results:

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented for DSST score by treatment group. The participant's DSST score is the number of correct items in 120 seconds, i.e. (the number of items were completed – the number of items were incorrect).

Change from baseline in the DSST Score from baseline to the second PSG visit will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

This analysis will be carried out for following treatment comparison

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm

3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

4.11.2 Delayed Word Recall Test (DWRT) Results

Summary information (the number and percentage of subjects by visit and treatment) will be tabulated for total number word recalled (0-10) and not recalled (0-10).

Change from baseline in the total number of words recalled from baseline to the second PSG visit will be compared between 75/5 dose and placebo group using ANCOVA with treatment group as factor and baseline results as a covariate.

Adjusted means, Standard error (SE) of Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented

1. 75/1.5 dose arm vs Placebo arm
2. 25/5 dose arm vs Placebo arm
3. 75/5 dose arm vs. 75/1.5 dose arm
4. 75/5 dose arm vs. 25/5 dose arm
5. 75/1.5 dose arm vs 25/5 dose arm

4.11.3 PSG Parameters

PSG parameters are measured in accordance with the American Academy of Sleep Medicine (AASM) scoring manual (Version 2.4).

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values will be presented for the following PSG parameters by study visits and treatment group. Summary statistics based on change from baseline variable only provided for the key PSG parameter. (details will be provided in the TLFs shell document)

- Periodic limb movements per hour
- Total recording time, Time in Bed, Total Sleep Time, Sleep Onset Latency, REM Latency, Latency to Persistent Sleep, Wake After Persistent Sleep and Sleep Efficiency.
- Spontaneous arousals per hour during sleep, Respiratory arousals per hour of sleep, PLM arousals per hour of sleep, Total number of all arousals per hour.
- Average apnea duration, Central Apneas per hour, Mixed Apneas per hour, Obstructive Apneas per hour, Hypopneas per hour
- Average heart rate during TST, total time in minute that SaO_2 is less than 90% during TST, total time in minute that SaO_2 is less than 80% during TST, minimum oxygen saturation during TST, mean Sa O_2 during TST

4.12 Determination of Sample Size

The effect of the drug combination in OSA has been investigated in preliminary academic studies that provide an estimate of effect size in a population similar to the planned Phase 2 study population. Data from a single-night cross-over study showed that a high proportion

of participants, 8/9 (88.9%), with demographic characteristics matched to the planned enrollment criterion of the planned Phase 2 study (baseline AHI ≥20, Body Mass Index [BMI] between 18.5 and 40 kg/m^2, and age from 25 to 65 years) when treated with a combination of 80 mg atomoxetine and 5 mg oxybutynin achieved a clinically relevant threshold of at least a 50% improvement in AHI score. Using a proposed sample size of n=35 for each of the 4 treatment groups, given 90% power and 2-sided alpha of 0.05, the sample size is powered to detect a difference in proportion of responders between the high-dose group and placebo, assuming a response rate as low as 37% in the high-dose group (compared with the preliminary data that suggests response rate may be as high as 90%) and 5% in the placebo group, estimated based on typical test-retest variability of PSG. Alternatively, if test-retest variability of PSG is higher, resulting in a higher placebo response rate of 10%, the study retains 90% power assuming a response rate in the high-dose group of 46%. Participants that discontinue prior to the second PSG visit will not be replaced and will be considered non-responders.

4.13 Changes in the Conduct of the Study or Planned Analysis

Not applicable.

5 REFERENCES

[1] American Academy of Sleep Medicine (AASM) scoring manual (Version 2.4)
[2] Apnimed Delayed Word Recall Test
[3] Digit Symbol Substitution Test
[4] The Epworth Sleepiness Scale
[5] STOP-BANG Sleep Apnea Questionnaire

6 APPENDICES

6.1 Schedule of Assessments

Table 1 Schedule of Assessments

Procedures	Screening and Baseline PSG[1]			Treatment Period			Visit 5 EOS[2]	Notes
	Non-PSG Daytime Visit 1	PSG night and next morning, Visit 2	Blinded baseline placebo, at-home dosing	Double-blind study treatment, at-home Dosing	Daytime Visit 3	Visit 4 PSG Visit		
Trial Day (Visit Window)	**-28 to -3**	**-7 to -1[3]**	**1 to 2[4]**	**3 – 11 ± 2[5]**	**6[6]**	**12 ± 2[7]**	**26 ± 4**	
Pre-screening	X[8]							Determination of basic eligibility for the study
Informed consent[9]	X							
Consent for genetic testing for CYP2D6	X							
Inclusion and exclusion criteria	X							
Demography	X							
STOP-Bang Questionnaire	X							Only used for participants without a history of diagnosis of OSA or CPAP use
Physical exam	X							
Medical and surgical history	X							Includes drug and substance usage and psychiatric history
Blood sample for CYP2D6 genotype	X							
Serum pregnancy test (WOCBP only)	X						X	

Procedures	Screening and Baseline PSG[1]			Treatment Period			Visit 5 EOS[2]	Notes
	Non-PSG Daytime Visit 1	PSG night and next morning, Visit 2	Blinded baseline placebo, at-home dosing	Double-blind study treatment, at-home Dosing	Daytime Visit 3	Visit 4 PSG Visit		
Trial Day (Visit Window)	**-28 to -3**	**-7 to -1[3]**	**1 to 2[4]**	**3 – 11 ± 2[5]**	**6[6]**	**12 ± 2[7]**	**26 ± 4**	
Urine drugs of abuse[10] testing, ethanol testing	X							
Randomization		X						Randomization takes place the morning after PSG testing for participants that qualify
Medication distribution to participant, and study instructions and device		X						Prior to discharge morning after PSG
QHS self-administration of baseline placebo			X					2 nights of QHS placebo, at home, all participants; administer ~30 minutes prior to bedtime
International Prostate Symptom Scale	X							Male participants only
QHS administration of randomized study treatment (combination drug or placebo)				X		X		Total of 10 nights: 3 nights low dose (25 mg atomoxetine/ 1.5 mg oxybutynin) followed by 7 nights randomized study treatment for participants randomized to active drug; 10 nights placebo for participants randomized to placebo.
"Reminder" telephone call/message				X				Day 10, participants reminded about study procedures and upcoming PSG visit[11]
Clinical laboratory assessments (hematology,	X					X	X	

Procedures	Screening and Baseline PSG[1]			Treatment Period			Visit 5 EOS[2]	Notes
	Non-PSG Daytime Visit 1	PSG night and next morning, Visit 2	Blinded baseline placebo, at-home dosing	Double-blind study treatment, at-home Dosing	Daytime Visit 3	Visit 4 PSG Visit		
Trial Day (Visit Window)	**-28 to -3**	**-7 to -1[3]**	**1 to 2[4]**	**3 – 11 ± 2[5]**	**6[6]**	**12 ± 2[7]**	**26 ± 4**	
clinical chemistry and urinalysis)								
12-lead ECG	X						X	
Vital signs[12]	X				X	X	X	Visit 4 measure both pre-dose and post-awakening from PSG
AE/SAE monitoring		X	X	X	X	X	X	
Study Instruction Reminder					X			
Oximeter Battery Change					X			
Prior/concomitant medication monitoring						X	X	
Inpatient Polysomnography		X				X		
ESS	X	X				X		Measured to determine eligibility and as efficacy outcome on PSG nights
CSSA	X					X	X[13]	Item 17 of the CSSA is used to assess suicidality
Patient Global Impression-Severity		X				X		Measured evening of baseline PSG and Visit 4 PSG
Patient Global Satisfaction with Treatment							X	
Home Oximetry			X	X				Oximeter used all at-home dosing nights

Procedures	Screening and Baseline PSG[1]			Treatment Period			Visit 5 EOS[2]	Notes
	Non-PSG Daytime Visit 1	PSG night and next morning, Visit 2	Blinded baseline placebo, at-home dosing	Double-blind study treatment, at-home Dosing	Daytime Visit 3	Visit 4 PSG Visit		
Trial Day (Visit Window)	**-28 to -3**	**-7 to -1[3]**	**1 to 2[4]**	**3 – 11 ± 2[5]**	**6[6]**	**12 ± 2[7]**	**26 ± 4**	
Delayed Word Recall Test		X				X		Administer at similar time after awakening after each PSG
DSST		X				X		Administer at similar time after awakening after each PSG

Abbreviations: AE = adverse event; CPAP = continuous positive airway pressure; CSSA = Cocaine Selective Severity Assessment; CYP2D6 = cytochrome P450 2D6; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EOS = end of study; ESS = Epworth Sleepiness Scale; HIV = human immunodeficiency virus; ICF = informed consent form; IRB = Institutional Review Board; IRT = Interactive Response Technology; OSA = obstructive sleep apnea; PSG = polysomnography; QHS = 1 dose taken at bedtime; SAE = serious adverse event; STOP-Bang = Snoring, Tiredness, Observed apnea, Blood Pressure-Body mass index, Age, Neck circumference and Gender criteria; WOCBP = women of childbearing potential.

1 Following pre-screening, participants who meet basic eligibility requirements will be screened during a visit that includes non- PSG evaluations. Participants who otherwise are eligible will be scheduled for an overnight PSG study.

2 If a participant discontinues from the study, all EOS procedures should be performed at the discontinuation visit, within 48 hours of the last study dose.

3 Final study eligibility is determined the morning after the PSG exam, based on PSG and non-PSG findings, and enrolled participants are randomized and dispensed the study drug. The first dose of study drug should generally be taken that night; however, at the discretion of the investigator, the first night of study treatment dosing can occur up to 1 week later to accommodate scheduling of the on-drug PSG exam.

4 Trial day includes overnight through morning completion of endpoints.

5 Daily bedtime dosing (qhs in the protocol synopsis) continues through Visit 4 PSG night, i.e., through PSG visit window; final night of study treatment dosing is PSG night.

6 Can occur as late as day as Day 7, if necessary for scheduling.

7 Preference is for PSG Visit 4 to be on Day 12, but, if necessary to fit individual participant scheduling, may be ± 2 days.

8 Conducted prior to screening/PSG admission; per IRB-approved pre-screening procedures.

9 No trial-related assessment is to be carried out before the participant has signed the ICF. Any participant who provides informed consent will have a screening number assigned by the IRT system.

10 Includes amphetamine; barbiturates; benzodiazepines; buprenorphine/metabolite; cannabinoids, cocaine/metabolites; Methylenedioxymethamphetamine; methadone/metabolite; opiates; oxycodone/oxymorphone; phencyclidine; by enzyme-linked immunosorbent assay method; test sample is urine.

11 Participants must return to PSG lab with study medication, pulse oximeter and study diary.

12 Vital signs include the following: seated blood pressure, pulse, respiratory rate; AE collection refers to spontaneous AEs. Participants who experience systolic blood pressure ≥ 160, or diastolic blood pressure ≥ 100, or heart rate ≥ 120 beats per minute will be further evaluated.

13 If there are any responses to individual items at EOS Visit that are more than 4 points worse than baseline exam, CSSA is repeated by telephone at 1 week post EOS Visit.