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November 3, 2022

To: ClinicalTrials.gov

This is a cover page to the redacted clinical protocol for APN-002 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 clinical protocol is associated with NCT 03845023.

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

- IND number

Sincerely,

DocuSigned by:
Jeanne Brittain
Signer Name: Jeanne Brittain
Signing Reason: I am the author of this document
Signing Time: 11/3/2022 | 12:58:44 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 | 9:17:09 AM EST 35E78DD6A7F34F8AA557BB15D08339BC	11/7/2022

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Clinical Study Protocol, Final Version 1.4, Dated 04 Dec 2018

Clinical Study Protocol Amendment 1, Final Version 1.4, Dated 12 Apr 2019

Title Page

Protocol Title: 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

Protocol Number: APN-002

Amendment Number: Not applicable

Compound Number: AD036

Short Title: Dose Finding Study of AD036 in Obstructive Sleep Apnea

Sponsor Name and Legal Registered Address:

Apnimed, Inc.
19 Ware Street, #3
Cambridge, MA 02138

Regulatory Agency Identifying Number: IND 136752

Approval Date: 04-Dec-2018

Date and Version of Previous Protocol: Not applicable

Sponsor Signatory:

Lawrence Miller, MD
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12/20/18
Date

Medical Monitor Name and Contact Information: provided in the Study Reference Manual.

Table of Contents

1 Protocol Summary

1.1 Synopsis

Protocol Title: 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

Sponsor Study No.: APN-002

Phase 2

Sponsor: Apnimed, Inc.

Rationale:

At the doses used in the initial human studies of the AD036 combination (atomoxetine 80 mg/oxybutynin 5 mg), there was support for efficacy and safety in participants with obstructive sleep apnea (OSA). This Phase 2 clinical study will further examine the efficacy and safety of both similar and lower dose AD036 combinations 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 this combination.

Objectives and Endpoints

Objectives	Endpoints
Primary To assess the efficacy of 3 different fixed doses of AD036 (the combination of atomoxetine and oxybutynin) vs. placebo To evaluate safety and tolerability of the combination AD036	• AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. placebo • Spontaneous adverse events, including the post-dosing period • Physical exam and laboratory testing • DSST • Delayed Word Recall Test • CSSA, Modified for study treatment • Prospective Suicidality Assessment (item 17 "suicidality" of CSSA) • PSG parameters: heart rate, ECG, EEG, oximetry • Physical exam, vital signs, clinical laboratory assessment, ECG
Secondary To assess the efficacy of 3 different fixed doses of the combination of AD036 vs. placebo	High dose vs placebo, in order: • Percent change AHI, high-dose arm vs. placebo • AHI in supine position, proportion of participants with ≥50% reduction, PSG nights • Oxygen desaturation index (number of desaturations/hour ≥4% below baseline), proportion of participants with ≥50% reduction, at-home nights • ESS • PGI-S, OSA, PSG nights • AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. each low dose arm (atomoxetine 75 mg /oxybutynin 1.5 mg, and atomoxetine 25 mg/ oxybutynin 5 mg)
Tertiary/Exploratory	Unranked • Proportion of participants with ≥50% AHI decrease and final AHI<15/hour, PSG nights • Total time with SaO_2 <90%, PSG nights • Total time with SaO_2 <80%, PSG nights • Snoring index, PSG nights • Sleep stages distribution and % of time in the various sleep stages, PSG nights • Arousal index, PSG nights • Oxygen desaturation index, low-dose run-in vs baseline, at home nights • Proportion of apneas to hypopneas

Abbreviations: AHI = apnea-hypopnea index; CSSA = Cocaine Selective Severity Assessment; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; PGI-S = Participant Global Impression of Severity; PSG = polysomnography; SaO_2 = oxygen saturation.

Overall Design:

This is a 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 OSA documented by polysomnography (PSG). Participants will be randomized equally to receive 1 of 3 different fixed-dose combinations of oxybutynin and atomoxetine, or matching placebo. For all participants, there is an initial 2-night at-home blinded baseline period in which placebo is dosed. Following this baseline placebo period, participants randomized to any of the 3 study treatment arms receive 3 nights of a low-dose run-in of the combination, consisting of atomoxetine 25 mg/oxybutynin 1.5mg. In contrast, during this 3-night run-in period, participants randomized to placebo receive placebo. Following this 3-night run-in period, participants will receive the treatment to which they were randomized, i.e., 1 of the 3 different fixed-dose combinations of study treatment, or placebo. Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Study participants will undergo eligibility screening that will include an initial exam to determine whether non- PSG enrollment criteria are met, followed by a 1-night inpatient PSG test for participants who qualify based on non-PSG criteria. For participants who are eligible and enroll in the study, the screening PSG night will serve as the baseline measure for apnea-hypopnea index (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, participants will return for inpatient PSG. The primary efficacy endpoint is the proportion of participants with ≥50% reduction in AHI from screening/baseline to final day of treatment with study treatment (study Day 11±2).

Participants will return 2 weeks after the last dose for an end of study (EOS) Visit. No subsequent open-label extension is planned following the study.

Number of Participants:

Approximately 140 participants will be randomized to study treatment in equal ratio (1:1:1:1), 35 participants per arm, to 1 of 4 parallel treatment groups.

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

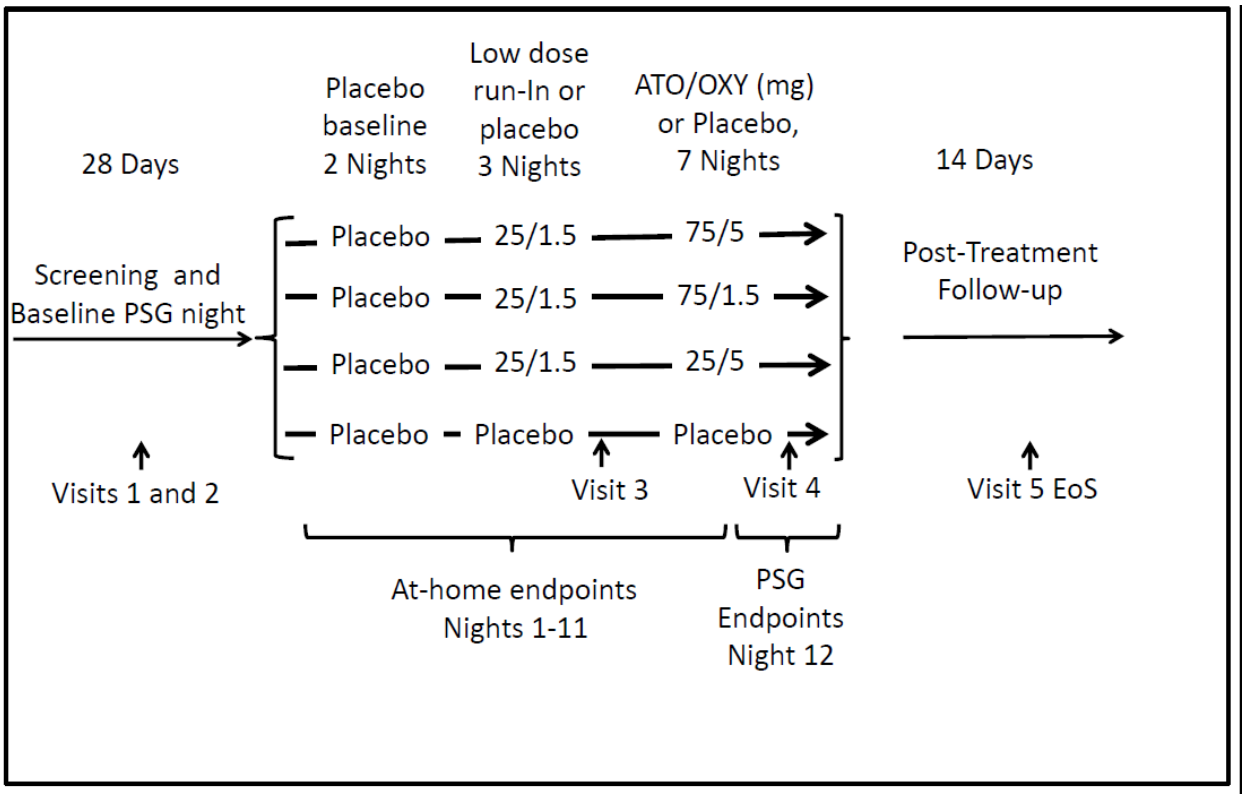
All participants will receive placebo for 2 days to establish baseline measures. Participants assigned to active treatment will subsequently receive low dose (25 mg atomoxetine/1.5 mg oxybutynin) for a 3-day dose-escalation period. Following the dose-escalation period, participants will receive the dose level to which they were randomized (75/5; 75/1.5; 25/5; placebo). Participants randomized to placebo will have a placebo run-in period.

The overall study duration will be up to 8 weeks, as follows:

- Up to 28 days for screening and baseline PSG;
- 2 nights of baseline placebo treatment, at home;
- 3 nights of low dose atomoxetine/oxybutynin, at home, for participants randomized to study treatment (participants randomized to placebo will receive placebo during this period);
- 7 (±2) nights of randomized study treatment; 6 nights at home, seventh night inpatient PSG;
- Follow-up safety visit, 2 weeks post study treatment dosing (±2 days), or upon early withdrawal.

1.2 Schema

Figure 1 Study Design Schema



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

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities

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		
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]

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		
Clinical laboratory assessments (hematology, clinical chemistry and urinalysis)	X					X	X	
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	

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		
Home Oximetry			X	X				Oximeter used all at-home dosing nights
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.

2 Introduction

2.1 Study Rationale

At the doses used in the initial human studies of the AD036 combination (atomoxetine 80 mg/oxybutynin 5 mg) there was support for efficacy and safety in patients with OSA. This Phase 2 clinical study will further examine the efficacy and safety both similar and lower dose AD036 combinations 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 this combination.

2.2 Background

2.2.1 Obstructive Sleep Apnea

The National Commission on Sleep Disorders Research identified sleep disorders as a major public health burden. OSA is the most common and serious of these sleep disorders and affects approximately 20 million people in the United States (US), with approximately 13% of men and 6% of women affected (Peppard et al, 2013). OSA is characterized by repetitive collapse or 'obstruction' of the pharyngeal airway during sleep, manifesting as repetitive episodes of hypopnea (i.e., shallow breathing) or apnea (i.e., paused breathing). These episodes of hypopnea or apnea may lead to arousal from sleep, sleep fragmentation, excessive daytime sleepiness, and/or neuropsychological impairment.

Research has shown that a number of pathogenic factors, or traits, contribute to the development of OSA (Eckert et al, 2013; Wellman et al, 2011; Wellman et al, 2013;Younes, 2003). The most important factors are the presence of an anatomically small, collapsible upper airway and a loss of pharyngeal muscle tone or responsiveness during sleep.

Long-term, OSA is associated with increased mortality and a number of adverse cardiovascular, neurocognitive, metabolic, and daytime functioning consequences (Somers et al, 1995; Nieto et al, 2000; Brooks et al, 1997; Peppard et al, 2000; Hung et al, 1990; Wessendorf et al, 2000; Hoffstein, 1994; Shahar et al, 2001; Redline et al, 1997; Findley et al, 1988).

2.2.2 Unmet Medical Need

Treatment for OSA changed little over the past 40 years, with the overwhelming majority of patients treated with positive airway pressure, the most common of which is continuous positive airway pressure (CPAP), provided by a machine that mechanically maintains an open airway. Other treatments, such as pharyngeal surgery, mandibular advancement devices, and implantable

nerve stimulators, were developed to address the anatomical predisposition to collapse; however, they have shown limited efficacy for niche populations.

While CPAP and related therapies are effective in improving sleep characteristics and oxygenation, many, perhaps most, patients find these devices uncomfortable or intolerable, and most estimates indicate that fewer than 50% of patients prescribed CPAP use it more than 4 hours per night, if at all (Weaver and Sawyer, 2010). Efforts to develop pharmacologic therapies, such as antidepressants, stimulants, and hormonal agents, for the treatment of OSA have been ongoing for at least 20 years, with no success thus far.

As many patients cannot use CPAP because they find it intolerable, this represents a significant health concern, as OSA is associated with numerous co-morbidities and increased mortality. Alternative options, such as drugs that activate the pharyngeal muscles are needed.

2.2.3 Biological Rationale

AD036 is a new fixed dose drug combination of atomoxetine and oxybutynin being developed for OSA. Atomoxetine is a pre-synaptic norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder in children and adults. Oxybutynin is an antispasmodic drug that inhibits the muscarinic action of acetylcholine on smooth muscle and is indicated for the treatment of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder such as urgency, frequency, urinary leakage, urge incontinence and dysuria.

Efficacy of the combination of these 2 small molecules for the signs and symptoms of OSA has been previously evaluated in a small number of patients in National Institutes of Health-supported studies in the academic setting. The pharmacokinetics (PK) of the atomoxetine and oxybutynin combination have recently been studied in a Phase 1 clinical program sponsored by Apnimed. New research in animals improved understanding of the state-dependent neurotransmitters involved in pharyngeal muscle activation during sleep, namely that both noradrenergic and antimuscarinic processes are involved. Specifically, the loss of noradrenergic activity is now thought to play a key role in the sleep-related hypotonia of pharyngeal muscles during non-rapid eye movement (NREM) sleep and muscarinic activity is involved in rapid eye movement (REM) atonia.

Chan and colleagues (Chan et al, 2006) showed in rats that the noradrenergic antagonist terazosin substantially reduced genioglossus (a major muscle of the upper airway) activity (i.e., genioglossal electromyographic [EMG_{gg}] activity) during wakefulness and produced REM-like atonia during NREM sleep, illustrating the importance of noradrenergic mechanisms. Other

studies (Lai et al, 2001; Fenik et al, 2005) also support the notion that progressive withdrawal of noradrenergic tone, from wakefulness to NREM and REM sleep, is the major mechanism causing sleep-related pharyngeal hypotonia. While noradrenergic withdrawal is thought to be the main cause of pharyngeal hypotonia in NREM sleep, there are additional mechanisms that cause further reduction during REM sleep. Chan and colleagues (Chan et al, 2006) failed to reverse REM atonia with alpha-1 receptor agonists applied to the hypoglossal nucleus, suggesting that another, possibly inhibitory, mechanism is at work. Horner and colleagues identified this inhibitory process as muscarinic by demonstrating restoration of EMG_{gg} activity during REM sleep with the muscarinic antagonist scopolamine applied directly to the hypoglossal nucleus in rats (Grace et al, 2013; Grace et al, 2013).

However, due to the only recent identification of these processes, until now there has not yet been an attempt to stimulate the pharyngeal muscles with both noradrenergic and antimuscarinic drugs in sleeping humans. Atomoxetine (a noradrenergic) and oxybutynin (an antimuscarinic) are 2 drugs within these pharmacologic classes that have been Food and Drug Administration-approved for over 16 years and 40 years, respectively, thereby having a long history of clinical use. Atomoxetine and oxybutynin as individual drugs have well-established PK, tolerability and safety profiles, but have not previously been studied in combination.

3 Objectives and Endpoints

Objectives	Endpoints
Primary To assess the efficacy of 3 different fixed doses of AD036 (the combination of atomoxetine and oxybutynin) vs. placebo	• AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. placebo
To evaluate safety and tolerability of the combination AD036	• Spontaneous adverse events, including the post-dosing period • Physical exam and laboratory testing • DSST • Delayed Word Recall Test • CSSA, Modified for study treatment • Prospective Suicidality Assessment (item 17 "suicidality" of CSSA) • PSG parameters: heart rate, ECG, EEG, oximetry • Physical exam, vital signs, clinical laboratory assessment, ECG
Secondary To assess the efficacy of 3 different fixed doses of AD036 vs. placebo	High dose vs placebo, in order: • Percent change AHI, high-dose arm vs. placebo • AHI in supine position, proportion of participants with ≥50% reduction, PSG nights • Oxygen desaturation index (number of desaturations/hour ≥4% below baseline), proportion of participants with ≥50% reduction, at-home nights • ESS • PGI-S, OSA, PSG nights • AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. each low dose arm (atomoxetine 75 mg /oxybutynin 1.5 mg, and atomoxetine 25 mg/ oxybutynin 5 mg).

Objectives	Endpoints
Tertiary/Exploratory	Unranked • Proportion of participants with ≥50% AHI decrease and final AHI<15/hour, PSG nights • Total time with SaO_2 <90%, PSG nights • Total time with SaO_2 <80%, PSG nights • Snoring index, PSG nights • Sleep stages distribution and % of time in the various sleep stages, PSG nights • Arousal index, PSG nights • Oxygen desaturation index, low-dose run-in vs baseline, at home nights • Proportion of apneas to hypopneas

Abbreviations: AHI = apnea-hypopnea index; CSSA = Cocaine Selective Severity Assessment; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; PGI-S = Participant Global Impression of Severity; PSG = polysomnography; SaO_2 = oxygen saturation.

4 Study Design

4.1 Overall Design

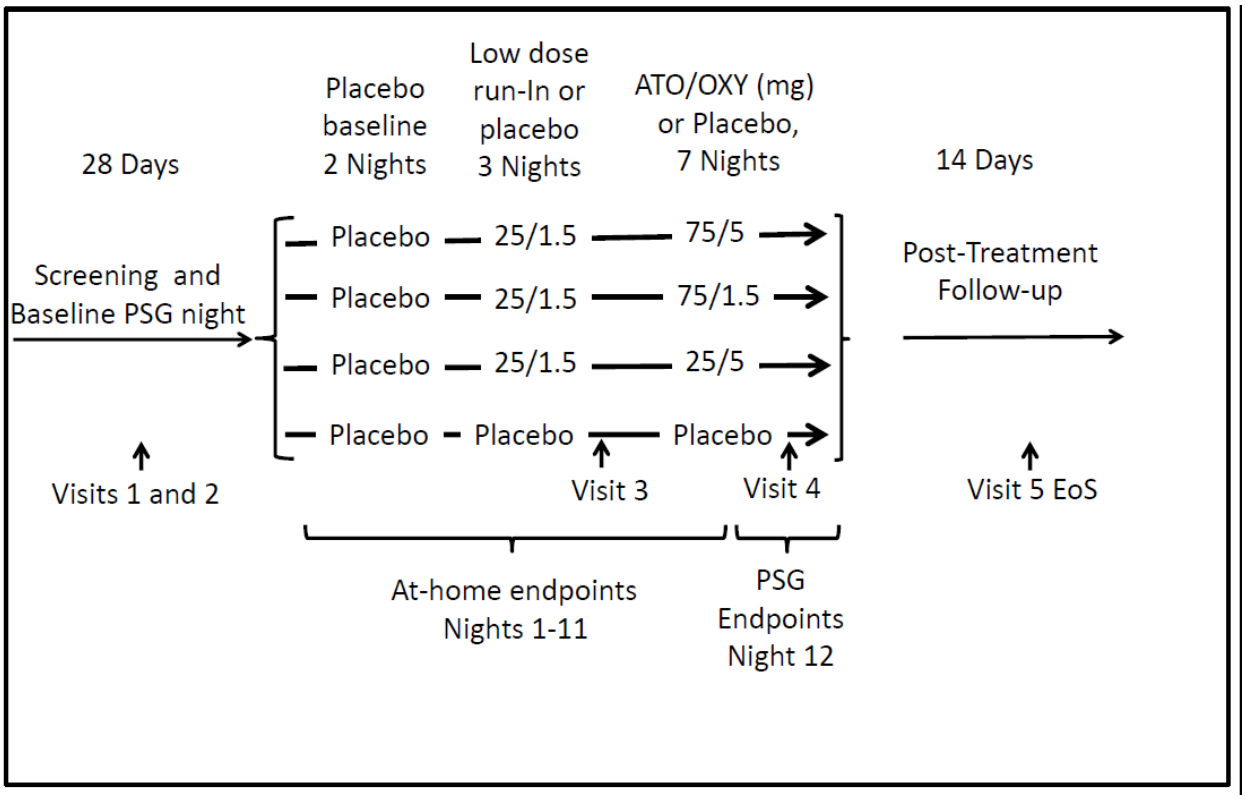
This is a randomized, double blind, placebo-controlled, repeat-dose, parallel arm, outpatient and inpatient, multi-center, dose finding study of the combination of atomoxetine and oxybutynin in adults with OSA documented by PSG. Approximately 140 participants will be randomized equally to receive 1 of 3 different fixed-dose combinations of oxybutynin and atomoxetine, or matching placebo. For all participants, there is an initial 2-night at-home blinded baseline period in which placebo is dosed. Following this baseline placebo period, participants randomized to the 3 study treatment arms receive 3 nights of a low-dose run-in of the combination, consisting of atomoxetine 25 mg/oxybutynin 1.5 mg. In contrast, during this 3-night run-in period, participants randomized to placebo receive placebo. Following this 3-night run-in period, participants will receive the treatment to which they were randomized, i.e., 1 of the 3 different fixed-dose combinations of drug, or placebo. Overall study duration will be up to 8-9 weeks. Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Study participants will undergo eligibility screening that will include an initial exam to determine whether non-PSG enrollment criteria are met, followed by a 1-night inpatient PSG test for participants who qualify based on non-PSG criteria. 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, participants will return for inpatient PSG. The primary efficacy endpoint is the proportion of participants with ≥50% reduction in AHI from screening/baseline to final day of treatment with study treatment (study Day 11± 2).

Participants will return 2 weeks after the last dose for an EOS Visit (Figure 2). No subsequent open-label extension is planned following the study.

Figure 2: Overview of Study Design



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

4.2 Scientific Rationale for Study Design

At the doses used in the initial human studies of AD036 there was support for efficacy and safety in patients with OSA. This Phase 2 clinical study will further examine the efficacy and safety of lower dose AD036 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 this combination.

4.3 Justification for Dose

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.

Prescribing information for atomoxetine specifies at least 3 days of dose escalation prior to dosing >40 mg. This study incorporates a 3-day dose escalation period using atomoxetine 25 mg/oxybutynin 1.5 mg for participants assigned to active drug in the randomized dosing period. Participants assigned to placebo in the randomized dosing period will correspondingly be dosed with placebo in the 3-day dose escalation period.

Prior to the dose escalation period all participants will be assigned to 2 days of placebo to establish baseline measures.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AD036 is provided in the Investigator's Brochure.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the final Follow-up visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

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.

5 Study Population

The study population will consist of male and female participants between 25 and 65 years of age, inclusive, with OSA documented by PSG. Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male or female participants between 25 to 65 years of age, inclusive, at the Screening Visit.

Type of Participant and Disease Characteristics

2. Participants are eligible for screening PSG if any of the following:

- Prior history of diagnosis of OSA of a severity for which CPAP is typically recommended (according to International Classification of Sleep Disorders, Version 3 criteria) at any time in the past (participant self-report acceptable if medical records unavailable); or, for participants without a prior diagnosis of OSA, participants are eligible for screening if the Snoring, Tiredness, Observed apnea, and Blood pressure (STOP), and Body mass index, Age, Neck circumference, and Gender (Bang) score is ≥5, or STOP ≥ 2 + body mass index (BMI) >35 kg/m^2.
- CPAP intolerance or poor compliance (compliance is defined as use of CPAP 4 hours per night for 70% of nights; per participant self-report); or CPAP-naïve.
- Participants who had been using CPAP at least 4 hours nightly for at least 70% of the nights are eligible for further screening and baseline PSG for this study only if CPAP will not have been used for 1 month prior to the screening/baseline PSG for this study.

3. AHI ≥ 20 on screening PSG, based on initial reading the night of Screening PSG[1].
4. Epworth Sleepiness Scale (ESS) score ≥ 8 for participants not using CPAP.
5. Previous surgical treatment for OSA is allowed if ≥ 1 year prior to enrollment.
6. If male, International Prostate Symptom Score (IPSS) must be less than 15.

Weight

7. BMI between 18.5 and 40.0 kg/m^2, inclusive, at the pre-PSG visit.

[1] The assessment of the PSG technician at the time of PSG recording is used to determine PSG eligibility criteria including AHI, central apnea index, and periodic limb movement arousal index; for the purposes of study endpoint analysis, the results of the PSG centralized reading will be used.

Male participants:

8. If male and sexually active with female partner(s) of childbearing potential, participant must agree, from Study Day 1 through 1 week after the last dose of study drug, to practice the protocol specified contraception (see Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information).

Female participants:

9. If a woman of childbearing potential (WOCBP), the participant must agree, from Study Day 1 through 1 week after the last dose of study drug, to practice the protocol specified contraception (See Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information). All WOCBP must have negative result of a serum pregnancy test performed at screening.
10. If female and of non-childbearing potential, the participant must be either postmenopausal (defined as age ≥ 55 years with no menses for 12 or more months without an alternative medical cause) or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Informed Consent

11. Participant voluntarily agrees to participate in this study and signs an Institutional Review Board (IRB)-approved informed consent prior to performing any of the Screening Visit procedures.
12. Participant must be able to understand the nature of the study and must have the opportunity to have any questions answered.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of narcolepsy.
2. Clinically significant craniofacial malformation.
3. Clinically significant cardiac disease (e.g., rhythm disturbances, coronary artery disease or cardiac failure) or hypertension requiring more than 2 medications for control.
4. Clinically significant neurological disorder, including epilepsy/convulsions.

5. History of schizophrenia, schizoaffective disorder or bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) or International Classification of Disease tenth edition criteria.
6. History of attempted suicide or suicidal ideation within 1 year prior to screening, or current suicidal ideation.
7. History of clinically significant constipation, gastric retention, or urinary retention.
8. Positive screen for drugs of abuse or substance use disorder as defined in DSM-V within 24 months prior to Screening Visit.
9. A significant illness or infection requiring medical treatment in the past 30 days.
10. Clinically significant cognitive dysfunction.
11. Untreated narrow angle glaucoma.
12. Women who are pregnant or nursing.

Prior/Concomitant Therapy

13. History of using oral or nasal devices for the treatment of OSA may enroll as long as the devices are not used during participation in the study.
14. History of using devices to affect participant sleeping position for the treatment of OSA, e.g. to discourage supine sleeping position, may enroll as long as the devices are not used during participation in the study.
15. History of oxygen therapy.
16. Use of medications from the list of disallowed concomitant medications.
17. Treatment with strong cytochrome P450 3A4 (CYP3A4) inhibitors, strong cytochrome P450 2D6 (CYP2D6) inhibitors, or monoamine oxidase inhibitors (MAOI) within 14 days of the start of treatment, or concomitant with treatment.

Prior/Concurrent Clinical Study Experience

18. Use of another investigational agent within 90 days or 5 half-lives, whichever is longer, prior to dosing.

Diagnostic Assessments

19. ESS total score > 18.

20. Central apnea index > 5/hour on baseline PSG.
21. Periodic limb movement arousal index >15/hour on baseline PSG.
22. Hepatic transaminases >3X the upper limit of normal (ULN), total bilirubin >2X ULN (unless confirmed Gilbert syndrome), serum creatinine >2X ULN.

Other Exclusions

23. <6 hours typical sleep duration.
24. Night- or shift-work sleep schedule.
25. Employment as a commercial driver or operator of heavy or hazardous equipment.
26. Smoking more than 10 cigarettes or 2 cigars per day.
27. Unwilling to use specified contraception.
28. Unwilling to limit alcohol consumption to no greater than 2 units/day or less, not to be consumed within 3 hours of bedtime.
29. Unwilling to limit caffeinated beverage intake (e.g., coffee, cola, tea) to 400 mg/day or less of caffeine, not to be used within 3 hours of bedtime.
30. Any condition that in the investigator's opinion would present an unreasonable risk to the participant, or which would interfere with their participation in the study or confound study interpretation.
31. Participant considered by the investigator, for any reason, an unsuitable candidate to receive AD036 or unable or unlikely to understand or comply with the dosing schedule or study evaluations.

5.3 Meals and Dietary Restrictions

1. Participants should refrain from consumption of any nutrients known to modulate CYP enzyme activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, pomegranate, and Seville or Moro [blood] orange products) within 72 hours before the first administration of study drug, during the study, and until final discharge.
2. Diet should be generally stable during the study, e.g., new diet programs should not be initiated.

5.4 Caffeine, Alcohol, and Tobacco

1. Participants should refrain from more than 2 units per day of alcohol, consumed no less than 3 hours prior to bedtime.
2. Moderate consumption of caffeinated beverages, containing up to a total of 400 mg caffeine per day, is permitted, consumed no less than 3 hours prior to bedtime.

5.5 Activity

There are no restrictions on physical activity during the study other than that physical activity should be generally stable during the study (e.g., new exercise programs should not be initiated).

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants that meets the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

6 Study 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.

6.1 Study Treatment(s) Administered

Two different blinded capsules are taken each night of drug treatment, as arranged in blister packaging. On placebo nights, 2 placebo tablets will be taken. On nights of randomized study treatment, 1 capsule of atomoxetine and 1 capsule of oxybutynin, or of corresponding placebo, are taken approximately 30 minutes before the participant's planned bedtime.

Study Treatment Name:	**Atomoxetine hydrochloride**	**Oxybutynin chloride**
Dosage Formulation:	Capsule	Capsule
Dosage Level:	75 mg or 25 mg	5 mg or 1.5 mg
Route of Administration:	Oral	Oral
Dosing Instructions:	1 capsule will be administered daily with at least 20 mL water	1 capsule will be administered daily with at least 20 mL water
Storage/Packaging/Labeling:	Store per package insert. Study treatment will be provided in blister packaging. Each blister package will be labeled as required per country requirement.	Store per package insert. Study treatment will be provided in blister packaging. Each blister package will be labeled as required per country requirement.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatments and only authorized site staff may supply or administer study treatments. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. After receiving Sponsor approval in writing, PAREXEL is 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.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized using an Interactive Response Technology (IRT). Each participant will be assigned a unique number (randomization number) that encodes the participant's assignment to 1 of the 4 arms of the study, according to the randomization schedule

generated by the Sponsor (or designee) using a validated computer program. Details of the procedure are described in the IRT Manual provided to all sites.

Study treatment will be dispensed the morning after PSG screening, as summarized in Section 1.3.

Returned study treatment should not be redispensed to the participants.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. If a participant's study treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Participants will be randomly assigned in a 1:1:1:1 equal allocation ratio to receive 1 of 3 different study treatment doses or placebo, using permuted blocked randomization. Investigators will remain blinded to each participant's assigned study treatment throughout the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4 Study Treatment Compliance

Participants will be required to return any unused study treatment capsules at Visit 4. Unused capsules will be counted and recorded by study personnel to assess study treatment compliance.

6.5 Concomitant Therapy

Concomitant therapy with the following medications is disallowed:

- MAOIs or other drugs that affect monoamine concentrations (e.g., rasagiline) [MAOIs are contraindicated for use with atomoxetine]
- Selective Serotonin Reuptake Inhibitors (e.g., paroxetine)
- Selective Norephinephrine Reuptake Inhibitors (e.g., duloxetine)

- Norephinephrine Reuptake Inhibitors (e.g., reboxetine)
- Alpha-1 antagonists (e.g., tamsulosin)
- Tricyclic antidepressants (e.g., desipramine)
- CYP2D6 inhibitors
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Benzodiazepines and other anxiolytics
- Opioids
- Sedatives other than nonbenzodiazepine "Z-drugs" (zolpidem, zaleplon, eszopiclone)
- Muscle relaxants
- Pressor agents
- Drugs with clinically significant cardiac QT-interval prolonging effects
- Drugs known to lower seizure threshold (e.g., chloroquine)
- Amphetamines
- Antiepileptics
- Antiemetics
- Modafinil or armodafinil
- $Beta_2$ agonists, (e.g., albuterol)
- Antipsychotics
- Anticholinergics and anticholinesterase inhibitors, including drugs with substantial anticholinergic side effects, (e.g., first generation antihistamines)
- Sedating antihistamines
- Pseudoephedrine, phenylephrine, oxymetazoline
- Nicotine replacement products
- Most drugs for Parkinson's, Alzheimer's, Huntington's, Amyotrophic Lateral Sclerosis, or drugs for other neurodegenerative diseases

Medications that do not have substantial effects on the central nervous system (CNS), respiration, or muscle activity are generally allowed if dose and frequency is stable for 3 months

prior to enrollment and during the course of the study, including, but not necessarily limited to, the following drugs and drug classes:

- Antihypertensives (angiotensin-converting-enzyme/angiotensin II receptor blocker inhibitors, calcium channel blockers, spironolactone, hydrochlorothiazide, etc.)
- Statins
- Proton pump inhibitors and histamine h_2 receptor blockers
- Over-the-counter (OTC) antacids
- Non-sedating antihistamines (e.g., cetirizine, loratadine)
- Eszopiclone, zolpidem, or zaleplon
- Melatonin
- Non-steroidal anti-inflammatory drugs and acetaminophen
- Laxatives
- Erectile dysfunction drugs
- Inhaled corticosteroids (e.g., fluticasone)
- Antidiabetics
- Ocular hypotensives and other ophthalmics (e.g., timolol)
- Hormonal therapy (e.g., estrogen replacement or anti-estrogens) and hormonal contraceptives
- Thyroid medications
- Anticoagulants
- OTC topicals (e.g., topical pain relievers)
- Osteoporosis drugs

6.6 Dose Modification

Through protocol amendment, planned doses may be decreased on an individual or group basis according to emerging safety and tolerability data.

6.7 Treatment After the End of the Study

Not applicable. No subsequent open-label extension is planned following the study.
Study treatment will not be available after the end of study participation.

7 Discontinuation of Study Treatment and Participant Discontinuation

Refer to the SoA for data that are to be collected at the time of study discontinuation, during follow-up, and for any further evaluations that need to be completed.

7.1 Discontinuation of Study Treatment

If a clinically significant finding is identified, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an adverse event (AE).

7.2 Stopping Criteria

7.2.1 Individual Participant Stopping Criteria

- Incidents of abuse, diversion, or misuse of the study treatment.
- Incidents of clinical significance: hallucinations, amnesia, delusional thinking, delirium, manic symptoms, aggressive behavior, suicidality, homicidality, agitation, confusion, or convulsions/seizures.
- Participants reporting any SAE.
- Acute urinary obstruction.
- Any other AE that in the judgment of the Investigator necessitates the participant stopping to protect participant safety.

Participants discontinued from dosing will undergo end of study procedures with follow-up monitoring of the AE(s) as clinically indicated.

7.3 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- All participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.
- Participation may be terminated before completing the study and the reason recorded as follows:
    - Withdrawal due to AE
    - Withdrawal due to incident abuse, diversion, or misuse of the study treatment
    - Loss to follow-up
    - Participant withdrew consent at own request
    - Other

7.4 Loss of Participants to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record/eCRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.

- As protocol waivers or exemptions are not allowed with the exception of immediate safety concerns, these should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, excluding any extra assessments that may be required for safety or technical issues, will not exceed around 50 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, as per the Investigator or designee's discretion.

8.1 Efficacy Assessments

The Study Reference Manual provides detailed information for the various scales discussed in Section 8.1.1 through Section 8.1.6.

8.1.1 Efficacy Endpoint Scales

- The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in 8 different activities in recent times. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'. The questionnaire takes approximately 2 or 3 minutes to answer. The ESS is asked during screening as an enrollment criterion. The ESS is also used as a study efficacy outcome. The ESS is administered the day of the non-PSG screening and approximately the same time of day prior to PSG recordings.

- The Participant Global Impression of Severity (PGI-S) is a global index that may be used to rate the severity of a specific condition, (i.e., it is a single-state scale). The scale consists of a 1-item questionnaire designed to assess the participant's impression of disease severity. The scale is considered to have clinical relevance for the participant because it allows participants to respond based on factors that they judge to be the most important in their health status. The PGI-S is administered at the baseline/screening PSG Visit 2 and at PSG Visit 4. The PGI-S is administered at approximately the same time prior to each PSG recording.
- The Participant Global Satisfaction with Treatment scale consists of a 1-item questionnaire designed to assess the participant's satisfaction with the experimental treatment, considering both safety and efficacy. The scale is administered at the end of the study, at the EOS Visit.

8.1.2 Safety and Abuse Liability Scale

- The Cocaine Selective Severity Assessment **(**CSSA) was designed to measure cocaine withdrawal signs and symptoms during detoxification, and 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. The CSSA will be used in this study to identify psychiatric issues and to characterize the potential of the atomoxetine/oxybutynin combination to elicit withdrawal symptoms similar to those elicited by cocaine withdrawal. A modified version of the assessment will be used in this study to measure potential withdrawal signs and symptoms from the study treatment; "cocaine" will be replaced with "study drug". The scale is administered by clinical staff. A score of ≥3 on Item 17, or Investigator judgment that the patient is suicidal, will initiate further clinical evaluation and appropriate measures to protect participant safety. (Note: Questions 4 and 5 of the CSSA will not be asked at baseline).

8.1.3 Functional Endpoints

- The Digit Symbol Substitution Test (DSST) is a paper-and-pencil cognitive and psychomotor test that requires patients to identify and copy symbols that are matched to numbers according to an instruction key located at the top of the page. The DSST is commonly used to screen for impairment related to pharmaceuticals and is also sensitive to sleep restriction. The DSST is administered the morning after the inpatient PSG nights, at approximately the same time after awaking from each PSG.

- The Delayed Word Recall Test (DWRT) is a brief and efficient test of verbal learning and recent memory. The DWRT is administered the morning after the screening/baseline PSG (Visit 2) and in the morning after PSG Visit 4. The DWRT is administered at approximately the same time after awaking from each PSG.

8.1.4 Screening/Eligibility Scales

- The IPSS is typically used to diagnose benign prostatic hyperplasia and to monitor disease progression and response to therapy. The participant is asked to choose the rating that best represents their condition. The scale ranges from 1 to 5, with 5 representing the most symptomatic disease and giving an overall maximum possible score of 35. The IPSS is administered to males as an enrollment criterion.
- The STOP-Bang questionnaire has been developed and validated as a screening tool for OSA. The STOP-Bang questionnaire is used in the study only for participants who do not have a previous diagnosis of OSA or use of CPAP, to determine whether there is a high enough pre-test probability of moderate to severe OSA to conduct enrollment screening. The standard STOP-Bang scoring used in the sleep clinic has only moderate specificity. For the purposes of this study, scoring with higher specificity is used (STOP-Bang score $\geq$5, or STOP $\geq$ 2 + BMI >35 kg/m^2) to decrease screening participants who are unlikely to meet enrollment criteria.

8.1.5 Polysomnography

- Methods: Standard overnight PSG recording and data interpretation will be performed in accordance with the American Academy of Sleep Medicine (AASM) scoring manual. Participants will be instrumented with standard PSG electrodes. Time of lights out will be established according to the participants' habitual schedule and kept constant across the PSG study nights. The participants will be given 8 hours of time-in bed.
- Technically Adequate Test: The screening/baseline PSG study must meet the following criteria for participants to enroll:
    - At least 4 hours of sleep.
    - At least 2 electroencephalograms (EEGs) and 2 electrooculography traces for the full night.
    - P nasal for at least 60% of the night and thermistor or both respiratory belts signals for the full night for scoring respiratory events.

- At least 30% of sleep in supine position.

Participants who do not have a technically adequate test at baseline can be retested at the discretion of the investigator.

- Scoring: For uses other than study enrollment, all studies will be scored by centralized PSG technologists, blinded to treatment assignment. Baseline and on-treatment PSGs for each individual participant will be scored by the same technologist. Scoring will be conducted according to the American Academy of Sleep Medicine manual scoring criteria.

8.1.6 Home Oximetry

- Participants will be instructed on the at-home use of oximetry at Visit 2 and will be provided with an oximeter that is capable of nightly recording and storage of data for the entire at-home period (study Days 1-11). Participant use of oximeter will be reinforced during the study visit on Day 6 (Visit 3), and through a reminder telephone contact on Day 10. The study personnel will replace the batteries in the oximeter during the Day 6 study visit. The number per hour of oxygen desaturations $\geq 4\%$ will be compared between the average of the baseline nights and the average of the randomized study treatment nights.

8.2 Safety Assessments

- Planned time points for all safety assessments are provided in the SoA.
- 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, as indicated by the initial data described above, 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 CNS effects such as memory difficulty. Safety monitoring will therefore include psychomotor vigilance testing and memory testing.

8.2.1 Physical Examinations

- Physical examinations at screening/baseline include anthropomorphic data relevant to OSA: neck circumference at superior border of cricothyroid cartilage; waist circumference at highest point of iliac crest; evaluation of the oropharynx, hypopharynx, and facial skeletal structure; Mallampati score; tonsils evaluation (0-3+); presence of micrognathia; nasal patency.
- The general physical examination at screening/baseline includes an assessment of general appearance and a review of physical systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems). Height and weight will also be measured and recorded (with shoes removed and wearing light indoor clothing).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Assessment of vital signs (seated blood pressure, pulse rate, body temperature, respiratory rate) will be performed at the time points indicated in the SoA (Section 1.3).
- Vital signs will be measured at all visits in a seated position after 5 minutes rest and will include temperature, respiratory rate, systolic and diastolic blood pressure, and pulse. Measurements should be made in the same arm of the participant at each visit.
- Systolic and diastolic blood pressure will be repeated for a total of 3 measurements, each at least 2 minutes apart.
- The method used to measure body temperature at screening should be maintained throughout the study for each participant, and should be indicated (e.g., ear, mouth, armpit).

8.2.3 Electrocardiograms

- A 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures the PR, QRS, and QT intervals, and the corrected QT-interval (QTc). The ECG will be recorded in the semi-supine position after the participant has rested in this position for at least 10 minutes.

8.2.4 Clinical Safety Laboratory Assessments

- Refer to Appendix 10.2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically relevant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from laboratory assessments not specified in the protocol and performed at the institution's local laboratory result in the need for a change in participant management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded in the eCRF.

8.2.5 Suicide Risk Monitoring

Atomoxetine and oxybutynin are CNS-active drugs. There has been concern that some CNS-active drugs may be associated with an increased risk of suicidal ideation or behavior when given to participants with certain conditions or baseline characteristics. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to adults, it is important to monitor for such events during this clinical study.

Suicidal ideation in children and adolescents is a boxed warning for atomoxetine; however, analysis in adult participants, the target population for the proposed OSA study, did not reveal an increased risk of suicidal ideation or behavior in association with atomoxetine.

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 and will initiate further clinical evaluation and appropriate measures to protect participant safety. Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing participants who experience signs of suicidal ideation or behavior. Families and caregivers of participants should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

8.3 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study and/or study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of informed consent form (ICF) until Visit 5/EOS at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably

related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification (within 24 hours, see Appendix 3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- 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.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

If a female partner of a male study participant who has been exposed to the study treatment becomes pregnant, the pregnancy and outcome of pregnancy should be monitored.

8.4 Treatment of Overdose

For this study, any dose of atomoxetine greater than 75 mg and of oxybutynin greater than 5 mg more frequently than QHS will be considered an overdose.

In the event of an overdose, the Investigator should refer to the approved product label for advice on overdose and:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until atomoxetine hydrochloride and/or oxybutynin chloride can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case by case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Genetics

A genetic sample will be taken during Treatment Period 1 only, on the screening/baseline visit (prior to randomization) to test for CYP2D6 poor metabolizers.

9 Statistical Considerations

9.1 Statistical Hypotheses

The null hypothesis is no change in the proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit (Visit 4) in the 75 mg/5 mg dose group compared with placebo.

9.2 Sample Size Determination

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, 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.

9.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who signed the ICF (including screening failures).
Modified Intent to Treat (mITT) Population	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. Participants will be analyzed for efficacy according to the treatment group into which they are randomized.
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 for safety based on the treatment received. A precise definition of "as actually received" will be added in the Statistical Analysis Plan (SAP).
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.

The primary endpoint comparison between the high dose (75/5) and placebo will consider all mITT participants randomized to those 2 groups; participants not returning for their second PSG night will be considered treatment non-responders.

9.4 Primary and Secondary Analyses

The SAP will be developed and finalized prior to database lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints. Further details are presented in the SAP.

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. OSA is often more severe in the supine sleeping position, and variability in time spent in the supine position between baseline and during on-drug PSG tests can otherwise introduce variability.
- 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 ESS from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
- Change from baseline in the 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 compared with the lower treatment dose of 75/1.5.

9.5 Interim Analyses

No formal interim analysis is planned.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
    - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.

    - Applicable laws and regulations.

- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
    - Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC guidelines, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the participant or the participant's legally authorized representative.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

When the clinical study report is completed, the Sponsor will provide the major findings of the study to the Investigator. A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinTrials.gov). The results may also be submitted for publication.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will lock the database.

- The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.11.1.

10.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

10.1.9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the US Investigational New Drug (IND) under which the study is being conducted.

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.11.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC/eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The EDC/eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the EDC/eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures PAREXEL and the Sponsor of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Laboratory testing is performed non-fasting.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 2: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Platelet Count RBC Count	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Basophils Eosinophils Lymphocytes Neutrophils Monocytes
Serum Chemistry	Albumin BUN Creatinine Potassium Sodium Total and direct bilirubin Total Protein Uric acid	ALT AST Alkaline phosphatase Calcium γGTP Glucose Total cholesterol Chloride Bicarbonate	
Routine Urinalysis	Specific gravity pH, protein (albumin), glucose, ketones, blood (RBC), WBC by dipstick Microscopic examination (if blood or protein is abnormal)		
Other Tests	• HbA1c (Screening Visit only) • CYP2D6 genotype • Serum hCG pregnancy test at screening and urine hCG tests at baseline. Additional testing may be performed if needed in WOCBP. • Alcohol and drugs of abuse screening		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CYP2D6 = cytochrome P450 2D6; γ-GTP = gamma guanosine-5'-triphosphate; HbA1c = hemoglobin A1c (glycated hemoglobin); hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell count; WBC = white blood cell; WOCBP = women of childbearing potential.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• 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. • NOTE: 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.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the PAREXEL Clinical Studies Safety Center. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the PAREXEL Clinical Studies Safety Center. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of 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.

Assessment of Causality
• 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 Clinical Studies Safety Center. 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 PAREXEL Clinical Studies Safety Center.**
- 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.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by PAREXEL Clinical Studies Safety Center to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide PAREXEL with a copy of any post-mortem

findings including histopathology.

- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to PAREXEL Clinical Studies Safety Center within 24 hours of receipt of the information.

Reporting of SAE to PAREXEL Clinical Studies Safety Center

SAE Reporting to PAREXEL Clinical Studies Safety Center Via EDC Tool
• The Investigator must report any SAEs to the PAREXEL Clinical Studies Safety Center within 24 hours of becoming aware of the event. • When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title. • The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/PAREXEL will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents (Investigator's Brochure or US product labeling for atomoxetine or oxybutynin). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
Any AE that is serious, associated with the use of the study treatment, and unexpected (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with study treatment, and unexpected, regulatory authorities and IECs will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study treatment, and unexpected, regulatory authorities and IECs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of participants. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

Reporting Serious Adverse Events

The Investigator must report any SAEs to the PAREXEL Clinical Studies Safety Center within 24 hours of becoming aware of the event.

When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/PAREXEL will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents (Investigator's Brochure or US product labeling for atomoxetine or oxybutynin). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from signing of informed consent until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally-related to study treatment.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

PAREXEL International Corporation
Clinical Studies Safety Center

The names and contact information for SAE reporting
will be provided in the Study Reference Manual.

1. Telephone the Medical Monitor/Drug Safety Specialist to inform him/her that you are faxing an SAE form. If the Medical Monitor is not available or you are calling after business hours (8:30 am to 5:30 pm Eastern time, Monday to Friday), leave a message in his/her voice mailbox.

2. Provide the Medical Monitor with the Principal Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

3. Fax the completed SAE form and any supporting documentation within 24 hours of becoming aware of the event to the email address or fax number listed on the SAE reporting form (investigator site file).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

WOCBP

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

NOTE: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Post-menopausal female

   - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

Contraception Guidance:

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if the agree to ONE of the following during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study treatment.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or to use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods That Are User Dependent[1] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent[1]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

1 Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- An additional serum pregnancy testing should be performed at Visit 5 (EOS).

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect any follow up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported, regardless of fetal state (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: List of Abbreviations

AHI	apnea-hypopnea index
AE	adverse event
Bang	Body mass index, Age, Neck circumference, and Gender criteria
BMI	body mass index
CFR	Code of Federal Regulations
CNS	central nervous system
CPAP	continuous positive air pressure
CSSA	Cocaine Selective Severity Assessment
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
EEG	electroencephalogram
eCRF	electronic case report form(s)
EDC	electronic data capture
EMG_{gg}	genioglossal electromyographic
EOS	end of study
ESS	Epworth Sleepiness Scale
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
OSA	obstructive sleep apnea
OTC	over-the-counter
MAOI	monoamine oxidase inhibitor
NREM	non-rapid eye movement
PGI-S	Participant Global Impression of Severity

PK	pharmacokinetic(s)
PSG	polysomnography
DWRT	Delayed Word Recall Test
QHS	1 dose every night at bedtime
REM	rapid eye movement
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
STOP	Snoring, Tiredness, Observed apnea, and Blood pressure criteria
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential

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Declaration of the Investigator

Title: 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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, EDC system/eCRF, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Title Page

Protocol Title: 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

Protocol Number: APN-002

Amendment Number: 1

Compound Number: AD036

Short Title: Dose Finding Study of AD036 in Obstructive Sleep Apnea

Sponsor Name and Legal Registered Address:

Apnimed, Inc.
19 Ware Street, #3
Cambridge, MA 02138

Regulatory Agency Identifying Number: IND 136752

Approval Date: 12 April 2019

Date and Version of Previous Protocol: 04 December 2018

Sponsor Signatory:

Lawrence Miller, MD
Chief Executive Officer

Date 4/4/19

Medical Monitor Name and Contact Information: provided in the Study Reference Manual.

Summary of Changes for IND 136752
Protocol APN-002
Version 1.4 (December 2018) to Version 1.4, Amendment 1 (April 2019)

Section	Description of Change	Rationale
Title Page	Protocol approval date	Protocol amendment
Table of Contents	Revised per contents	Reflects revised contents
1.1 Synopsis	Minor editorial changes	Increase clarity
1.3 Schedule of Activities	a) Visit 1 window changed from day -28 to -3 to day -28 to -1	a) Visit 1 activities can occur through day -1
	b) Drug of Abuse: Oxycodone/oxymorphone test removed	b) Test is for opiates
	c) AE/SAE monitoring added at Visit 1	c) AE/SAE collected after signing informed consent
	d) Reminder phone call changed from day 10 to day 10 ± 2	d) To align with Visit 4 PSG window
	e) Prior/concomitant medication monitoring added to Visit 3	e) Prior/concomitant medication monitoring takes place at Visit 3
	f) ESS measured evening of baseline PSG and Visit 4 PSG	f) Clarify time of administration
3 Objectives and Endpoints	Minor editorial changes	Increase clarity
4.1 Overall Design	final day of treatment corrected to day 12± 2	Typographical error
Inclusion criterion 1 Age range	Increase maximum enrollment age of women from 65 to 70 years	Upper age limit had been based on risk of urinary retention related to benign prostatic hypertrophy, which is not a factor in women
Inclusion criterion 4 Epworth Sleepiness Scale	Minimum score required for enrollment reduced from 8 to 4	Score of 8 was unnecessarily restrictive of enrollment
5.6 Screen Failures	Allow rescreening if enabled by a protocol amendment	Patient for screening becomes fully compliant with the amended protocol
6.5 Concomitant therapy	Minor spelling errors corrected	Typographical error

Table of Contents

1 Protocol Summary

1.1 Synopsis

Protocol Title: 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

Sponsor Study No.: APN-002

Phase 2

Sponsor: Apnimed, Inc.

Rationale:

At the doses used in the initial human studies of the AD036 combination (atomoxetine 80 mg/oxybutynin 5 mg), there was support for efficacy and safety in participants with obstructive sleep apnea (OSA). This Phase 2 clinical study will further examine the efficacy and safety of both similar and lower dose AD036 combinations 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 this combination.

Objectives and Endpoints

Objectives	Endpoints
Primary To assess the efficacy of 3 different fixed doses of AD036 (the combination of atomoxetine and oxybutynin) vs. placebo To evaluate safety and tolerability of the combination AD036	Primary Efficacy Endpoint • AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. placebo Safety Endpoints • Spontaneous adverse events, including the post-dosing period • Physical exam and laboratory testing • DSST • Delayed Word Recall Test • CSSA, Modified for study treatment • Prospective Suicidality Assessment (item 17 "suicidality" of CSSA) • PSG parameters: heart rate, ECG, EEG, oximetry • Physical exam, vital signs, clinical laboratory assessment, ECG
Secondary To assess the efficacy of 3 different fixed doses of the combination of AD036 vs. placebo	Secondary Efficacy Endpoints High dose vs placebo, in order: • Percent change AHI, high-dose arm vs. placebo • AHI in supine position, proportion of participants with ≥50% reduction, PSG nights • Oxygen desaturation index (number of desaturations/hour ≥4% below baseline), proportion of participants with ≥50% reduction, at-home nights • ESS • PGI-S, OSA, PSG nights • AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. each low dose arm (atomoxetine 75 mg /oxybutynin 1.5 mg, and atomoxetine 25 mg/ oxybutynin 5 mg)
Tertiary/Exploratory	Unranked Efficacy Endpoints • Proportion of participants with ≥50% AHI decrease and final AHI<15/hour, PSG nights • Total time with SaO_2 <90%, PSG nights • Total time with SaO_2 <80%, PSG nights • Snoring index, PSG nights • Sleep stages distribution and % of time in the various sleep stages, PSG nights • Arousal index, PSG nights • Oxygen desaturation index, low-dose run-in vs baseline, at home nights • Proportion of apneas to hypopneas

Abbreviations: AHI = apnea-hypopnea index; CSSA = Cocaine Selective Severity Assessment; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; PGI-S = Participant Global Impression of Severity; PSG = polysomnography; SaO_2 = oxygen saturation.

Overall Design:

This is a 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 OSA documented by polysomnography (PSG). Participants will be randomized equally to receive 1 of 3 different fixed-dose combinations of oxybutynin and atomoxetine, or matching placebo. For all participants, there is an initial 2-night at-home blinded baseline period in which placebo is dosed. Following this baseline placebo period, participants randomized to any of the 3 study treatment arms receive 3 nights of a low-dose run-in of the combination, consisting of atomoxetine 25 mg/oxybutynin 1.5mg. In contrast, during this 3-night run-in period, participants randomized to placebo receive placebo. Following this 3-night run-in period, participants will receive the treatment to which they were randomized, i.e., 1 of the 3 different fixed-dose combinations of study treatment, or placebo. Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Study participants will undergo eligibility screening that will include an initial exam to determine whether non- PSG enrollment criteria are met, followed by a 1-night inpatient PSG test for participants who qualify based on non-PSG criteria. For participants who are eligible and enroll in the study, the screening PSG night will serve as the baseline measure for apnea-hypopnea index (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, participants will return for inpatient PSG. The primary efficacy endpoint is the proportion of participants with ≥50% reduction in AHI from screening/baseline to final day of treatment with study treatment (study Day 11±2).

Participants will return 2 weeks after the last dose for an end of study (EOS) Visit. No subsequent open-label extension is planned following the study.

Number of Participants:

Approximately 140 participants will be randomized to study treatment in equal ratio (1:1:1:1), 35 participants per arm, to 1 of 4 parallel treatment groups.

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

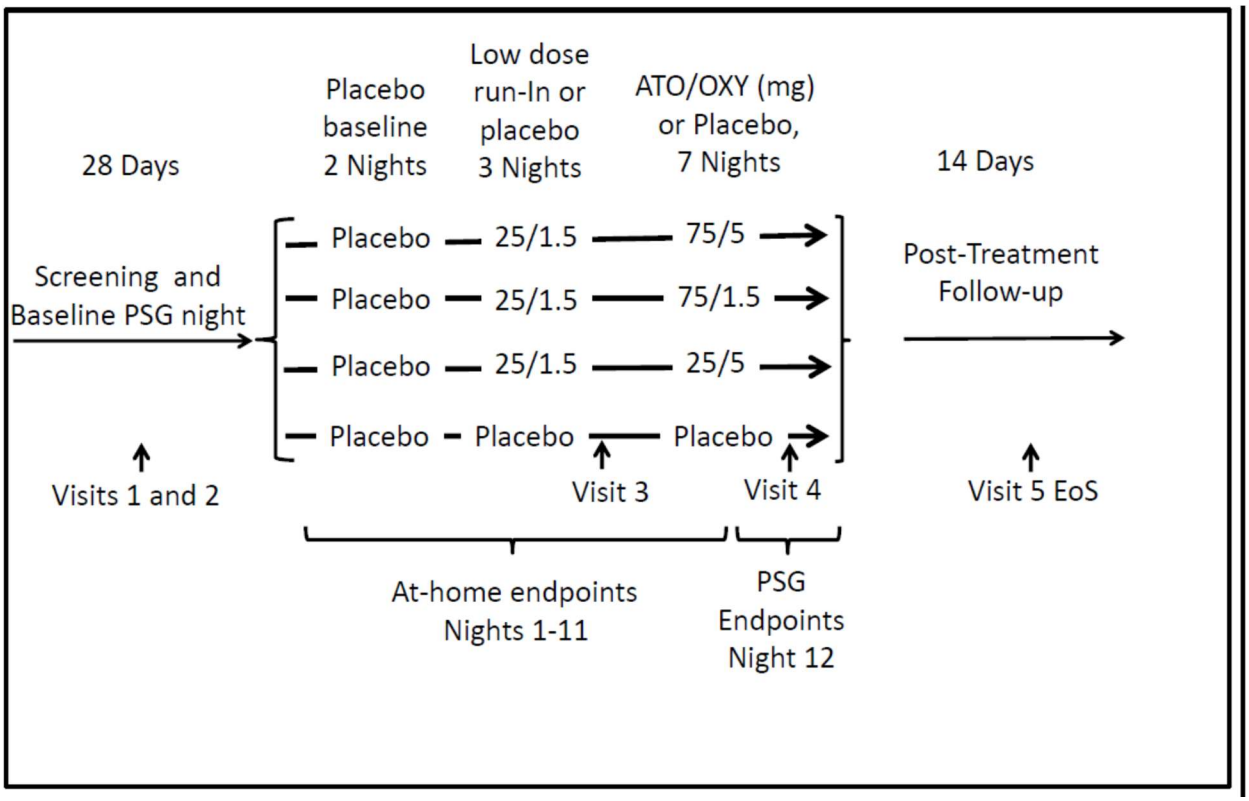
All participants will receive placebo for 2 days to establish baseline measures. Participants assigned to active treatment will subsequently receive low dose (25 mg atomoxetine/1.5 mg oxybutynin) for a 3-day dose-escalation period. Following the dose-escalation period, participants will receive the dose level to which they were randomized (75/5; 75/1.5; 25/5; placebo). Participants randomized to placebo will have a placebo run-in period.

The overall study duration will be up to 8 weeks, as follows:

- Up to 28 days for screening and baseline PSG;
- 2 nights of baseline placebo treatment, at home;
- 3 nights of low dose atomoxetine/oxybutynin, at home, for participants randomized to study treatment (participants randomized to placebo will receive placebo during this period);
- 7 (±2) nights of randomized study treatment; 6 nights at home, seventh night inpatient PSG;
- Follow-up safety visit, 2 weeks post study treatment dosing (±2 days), or upon early withdrawal.

1.2 Schema

Figure 1 Study Design Schema



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

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities

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 -1**	**-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	

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±2, participants reminded about study procedures and upcoming PSG visit[11]
Clinical laboratory assessments (hematology, clinical chemistry and urinalysis)	X					X	X	
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	X	
Study Instruction Reminder					X			
Oximeter Battery Change					X			
Prior/concomitant medication monitoring					X	X	X	
Inpatient Polysomnography		X				X		
ESS	X	X				X		Measured at Visit 1 to determine eligibility and as efficacy outcome on PSG nights; measured evening of baseline PSG and Visit 4 PSG
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
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;; 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.

2 Introduction

2.1 Study Rationale

At the doses used in the initial human studies of the AD036 combination (atomoxetine 80 mg/oxybutynin 5 mg) there was support for efficacy and safety in patients with OSA. This Phase 2 clinical study will further examine the efficacy and safety both similar and lower dose AD036 combinations 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 this combination.

2.2 Background

2.2.1 Obstructive Sleep Apnea

The National Commission on Sleep Disorders Research identified sleep disorders as a major public health burden. OSA is the most common and serious of these sleep disorders and affects approximately 20 million people in the United States (US), with approximately 13% of men and 6% of women affected (Peppard et al, 2013). OSA is characterized by repetitive collapse or 'obstruction' of the pharyngeal airway during sleep, manifesting as repetitive episodes of hypopnea (i.e., shallow breathing) or apnea (i.e., paused breathing). These episodes of hypopnea or apnea may lead to arousal from sleep, sleep fragmentation, excessive daytime sleepiness, and/or neuropsychological impairment.

Research has shown that a number of pathogenic factors, or traits, contribute to the development of OSA (Eckert et al, 2013; Wellman et al, 2011; Wellman et al, 2013;Younes, 2003). The most important factors are the presence of an anatomically small, collapsible upper airway and a loss of pharyngeal muscle tone or responsiveness during sleep.

Long-term, OSA is associated with increased mortality and a number of adverse cardiovascular, neurocognitive, metabolic, and daytime functioning consequences (Somers et al, 1995; Nieto et al, 2000; Brooks et al, 1997; Peppard et al, 2000; Hung et al, 1990; Wessendorf et al, 2000; Hoffstein, 1994; Shahar et al, 2001; Redline et al, 1997; Findley et al, 1988).

2.2.2 Unmet Medical Need

Treatment for OSA changed little over the past 40 years, with the overwhelming majority of patients treated with positive airway pressure, the most common of which is continuous positive airway pressure (CPAP), provided by a machine that mechanically maintains an open airway. Other treatments, such as pharyngeal surgery, mandibular advancement devices, and implantable

nerve stimulators, were developed to address the anatomical predisposition to collapse; however, they have shown limited efficacy for niche populations.

While CPAP and related therapies are effective in improving sleep characteristics and oxygenation, many, perhaps most, patients find these devices uncomfortable or intolerable, and most estimates indicate that fewer than 50% of patients prescribed CPAP use it more than 4 hours per night, if at all (Weaver and Sawyer, 2010). Efforts to develop pharmacologic therapies, such as antidepressants, stimulants, and hormonal agents, for the treatment of OSA have been ongoing for at least 20 years, with no success thus far.

As many patients cannot use CPAP because they find it intolerable, this represents a significant health concern, as OSA is associated with numerous co-morbidities and increased mortality. Alternative options, such as drugs that activate the pharyngeal muscles are needed.

2.2.3 Biological Rationale

AD036 is a new fixed dose drug combination of atomoxetine and oxybutynin being developed for OSA. Atomoxetine is a pre-synaptic norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder in children and adults. Oxybutynin is an antispasmodic drug that inhibits the muscarinic action of acetylcholine on smooth muscle and is indicated for the treatment of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder such as urgency, frequency, urinary leakage, urge incontinence and dysuria.

Efficacy of the combination of these 2 small molecules for the signs and symptoms of OSA has been previously evaluated in a small number of patients in National Institutes of Health-supported studies in the academic setting. The pharmacokinetics (PK) of the atomoxetine and oxybutynin combination have recently been studied in a Phase 1 clinical program sponsored by Apnimed. New research in animals improved understanding of the state-dependent neurotransmitters involved in pharyngeal muscle activation during sleep, namely that both noradrenergic and antimuscarinic processes are involved. Specifically, the loss of noradrenergic activity is now thought to play a key role in the sleep-related hypotonia of pharyngeal muscles during non-rapid eye movement (NREM) sleep and muscarinic activity is involved in rapid eye movement (REM) atonia.

Chan and colleagues (Chan et al, 2006) showed in rats that the noradrenergic antagonist terazosin substantially reduced genioglossus (a major muscle of the upper airway) activity (i.e., genioglossal electromyographic [EMG_{gg}] activity) during wakefulness and produced REM-like atonia during NREM sleep, illustrating the importance of noradrenergic mechanisms. Other

studies (Lai et al, 2001; Fenik et al, 2005) also support the notion that progressive withdrawal of noradrenergic tone, from wakefulness to NREM and REM sleep, is the major mechanism causing sleep-related pharyngeal hypotonia. While noradrenergic withdrawal is thought to be the main cause of pharyngeal hypotonia in NREM sleep, there are additional mechanisms that cause further reduction during REM sleep. Chan and colleagues (Chan et al, 2006) failed to reverse REM atonia with alpha-1 receptor agonists applied to the hypoglossal nucleus, suggesting that another, possibly inhibitory, mechanism is at work. Horner and colleagues identified this inhibitory process as muscarinic by demonstrating restoration of EMG_{gg} activity during REM sleep with the muscarinic antagonist scopolamine applied directly to the hypoglossal nucleus in rats (Grace et al, 2013; Grace et al, 2013).

However, due to the only recent identification of these processes, until now there has not yet been an attempt to stimulate the pharyngeal muscles with both noradrenergic and antimuscarinic drugs in sleeping humans. Atomoxetine (a noradrenergic) and oxybutynin (an antimuscarinic) are 2 drugs within these pharmacologic classes that have been Food and Drug Administration-approved for over 16 years and 40 years, respectively, thereby having a long history of clinical use. Atomoxetine and oxybutynin as individual drugs have well-established PK, tolerability and safety profiles, but have not previously been studied in combination.

3 Objectives and Endpoints

Objectives	Endpoints
Primary To assess the efficacy of 3 different fixed doses of AD036 (the combination of atomoxetine and oxybutynin) vs. placebo To evaluate safety and tolerability of the combination AD036	Primary Efficacy Endpoint • AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. placebo Safety Endpoints • Spontaneous adverse events, including the post-dosing period • Physical exam and laboratory testing • DSST • Delayed Word Recall Test • CSSA, Modified for study treatment • Prospective Suicidality Assessment (item 17 "suicidality" of CSSA) • PSG parameters: heart rate, ECG, EEG, oximetry • Physical exam, vital signs, clinical laboratory assessment, ECG
Secondary To assess the efficacy of 3 different fixed doses of AD036 vs. placebo	Secondary Efficacy Endpoints High dose vs placebo, in order: • Percent change AHI, high-dose arm vs. placebo • AHI in supine position, proportion of participants with ≥50% reduction, PSG nights • Oxygen desaturation index (number of desaturations/hour ≥4% below baseline), proportion of participants with ≥50% reduction, at-home nights • ESS • PGI-S, OSA, PSG nights • AHI, proportion of participants with ≥50% reduction, PSG nights, high-dose (atomoxetine 75 mg/oxybutynin 5 mg) arm vs. each low dose arm (atomoxetine 75 mg /oxybutynin 1.5 mg, and atomoxetine 25 mg/ oxybutynin 5 mg).
Tertiary/Exploratory	Unranked Efficacy Endpoints • Proportion of participants with ≥50% AHI decrease and final AHI<15/hour, PSG nights • Total time with SaO_2 <90%, PSG nights • Total time with SaO_2 <80%, PSG nights • Snoring index, PSG nights • Sleep stages distribution and % of time in the various sleep stages, PSG nights • Arousal index, PSG nights • Oxygen desaturation index, low-dose run-in vs baseline, at home nights • Proportion of apneas to hypopneas
Abbreviations: AHI = apnea-hypopnea index; CSSA = Cocaine Selective Severity Assessment; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; PGI-S = Participant Global Impression of Severity; PSG = polysomnography; SaO_2 = oxygen saturation.	

4 Study Design

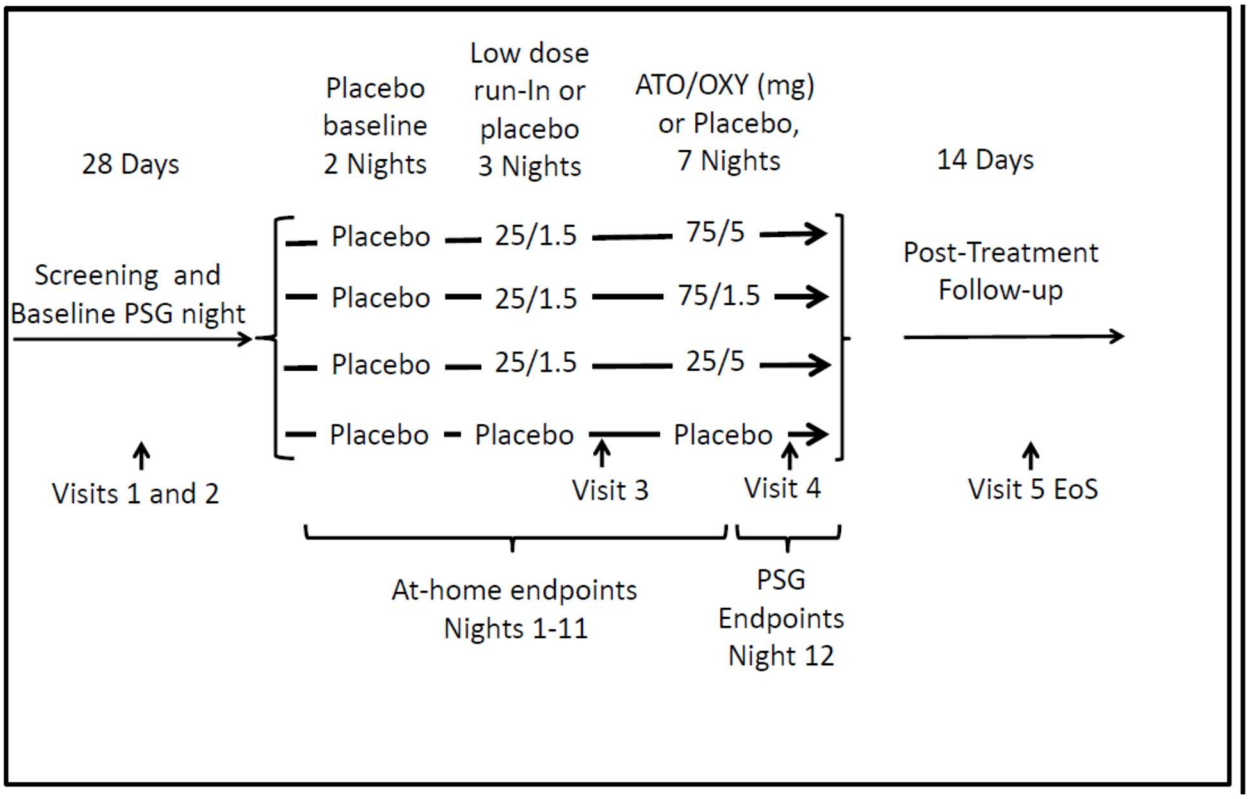
4.1 Overall Design

This is a 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 OSA documented by PSG. Approximately 140 participants will be randomized equally to receive 1 of 3 different fixed-dose combinations of oxybutynin and atomoxetine, or matching placebo. For all participants, there is an initial 2-night at-home blinded baseline period in which placebo is dosed. Following this baseline placebo period, participants randomized to the 3 study treatment arms receive 3 nights of a low-dose run-in of the combination, consisting of atomoxetine 25 mg/oxybutynin 1.5 mg. In contrast, during this 3-night run-in period, participants randomized to placebo receive placebo. Following this 3-night run-in period, participants will receive the treatment to which they were randomized, i.e., 1 of the 3 different fixed-dose combinations of drug, or placebo. Overall study duration will be up to 8-9 weeks. Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Study participants will undergo eligibility screening that will include an initial exam to determine whether non-PSG enrollment criteria are met, followed by a 1-night inpatient PSG test for participants who qualify based on non-PSG criteria. 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, participants will return for inpatient PSG. The primary efficacy endpoint is the proportion of participants with ≥50% reduction in AHI from screening/baseline to final day of treatment with study treatment (study Day 12± 2).

Participants will return 2 weeks after the last dose for an EOS Visit (Figure 2). No subsequent open-label extension is planned following the study.

Figure 2: Overview of Study Design



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

4.2 Scientific Rationale for Study Design

At the doses used in the initial human studies of AD036 there was support for efficacy and safety in patients with OSA. This Phase 2 clinical study will further examine the efficacy and safety of lower dose AD036 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 this combination.

4.3 Justification for Dose

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.

Prescribing information for atomoxetine specifies at least 3 days of dose escalation prior to dosing >40 mg. This study incorporates a 3-day dose escalation period using atomoxetine 25 mg/oxybutynin 1.5 mg for participants assigned to active drug in the randomized dosing

period. Participants assigned to placebo in the randomized dosing period will correspondingly be dosed with placebo in the 3-day dose escalation period.

Prior to the dose escalation period all participants will be assigned to 2 days of placebo to establish baseline measures.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AD036 is provided in the Investigator's Brochure.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the final Follow-up visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

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.

5 Study Population

The study population will consist of male and female participants between 25 and 65 years of age, inclusive, with OSA documented by PSG. Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male participants between 25 to 65 years of age or female participants between 25 to 70 years of age, inclusive, at the Screening Visit.

Type of Participant and Disease Characteristics

2. Participants are eligible for screening PSG if any of the following:

- Prior history of diagnosis of OSA of a severity for which CPAP is typically recommended (according to International Classification of Sleep Disorders, Version 3 criteria) at any time in the past (participant self-report acceptable if medical records unavailable); or, for participants without a prior diagnosis of OSA, participants are eligible for screening if the Snoring, Tiredness, Observed apnea, and Blood pressure (STOP), and Body mass index, Age, Neck circumference, and Gender (Bang) score is ≥5, or STOP ≥ 2 + body mass index (BMI) >35 kg/m^2.
- CPAP intolerance or poor compliance (compliance is defined as use of CPAP 4 hours per night for 70% of nights; per participant self-report); or CPAP-naïve.
- Participants who had been using CPAP at least 4 hours nightly for at least 70% of the nights are eligible for further screening and baseline PSG for this study only if CPAP will not have been used for 1 month prior to the screening/baseline PSG for this study.

3. AHI ≥ 20 on screening PSG, based on initial reading the night of Screening PSG[1].

[1] The assessment of the PSG technician at the time of PSG recording is used to determine PSG eligibility criteria including AHI, central apnea index, and periodic limb movement arousal index; for the purposes of study endpoint analysis, the results of the PSG centralized reading will be used.

4. Epworth Sleepiness Scale (ESS) score ≥ 4 for participants not using CPAP.
5. Previous surgical treatment for OSA is allowed if ≥ 1 year prior to enrollment.
6. If male, International Prostate Symptom Score (IPSS) must be less than 15.

Weight

7. BMI between 18.5 and 40.0 kg/m^2, inclusive, at the pre-PSG visit.

Male participants:

8. If male and sexually active with female partner(s) of childbearing potential, participant must agree, from Study Day 1 through 1 week after the last dose of study drug, to practice the protocol specified contraception (see Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information).

Female participants:

9. If a woman of childbearing potential (WOCBP), the participant must agree, from Study Day 1 through 1 week after the last dose of study drug, to practice the protocol specified contraception (See Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information). All WOCBP must have negative result of a serum pregnancy test performed at screening.
10. If female and of non-childbearing potential, the participant must be either postmenopausal (defined as age ≥ 55 years with no menses for 12 or more months without an alternative medical cause) or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Informed Consent

11. Participant voluntarily agrees to participate in this study and signs an Institutional Review Board (IRB)-approved informed consent prior to performing any of the Screening Visit procedures.
12. Participant must be able to understand the nature of the study and must have the opportunity to have any questions answered.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of narcolepsy.
2. Clinically significant craniofacial malformation.
3. Clinically significant cardiac disease (e.g., rhythm disturbances, coronary artery disease or cardiac failure) or hypertension requiring more than 2 medications for control.
4. Clinically significant neurological disorder, including epilepsy/convulsions.
5. History of schizophrenia, schizoaffective disorder or bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) or International Classification of Disease tenth edition criteria.
6. History of attempted suicide or suicidal ideation within 1 year prior to screening, or current suicidal ideation.
7. History of clinically significant constipation, gastric retention, or urinary retention.
8. Positive screen for drugs of abuse or substance use disorder as defined in DSM-V within 24 months prior to Screening Visit.
9. A significant illness or infection requiring medical treatment in the past 30 days.
10. Clinically significant cognitive dysfunction.
11. Untreated narrow angle glaucoma.
12. Women who are pregnant or nursing.

Prior/Concomitant Therapy

13. History of using oral or nasal devices for the treatment of OSA may enroll as long as the devices are not used during participation in the study.
14. History of using devices to affect participant sleeping position for the treatment of OSA, e.g. to discourage supine sleeping position, may enroll as long as the devices are not used during participation in the study.
15. History of oxygen therapy.
16. Use of medications from the list of disallowed concomitant medications.
17. Treatment with strong cytochrome P450 3A4 (CYP3A4) inhibitors, strong cytochrome P450 2D6 (CYP2D6) inhibitors, or monoamine oxidase inhibitors (MAOI) within 14 days of the start of treatment, or concomitant with treatment.

Prior/Concurrent Clinical Study Experience

18. Use of another investigational agent within 90 days or 5 half-lives, whichever is longer, prior to dosing.

Diagnostic Assessments

19. ESS total score > 18.
20. Central apnea index > 5/hour on baseline PSG.
21. Periodic limb movement arousal index >15/hour on baseline PSG.
22. Hepatic transaminases >3X the upper limit of normal (ULN), total bilirubin >2X ULN (unless confirmed Gilbert syndrome), serum creatinine >2X ULN.

Other Exclusions

23. <6 hours typical sleep duration.
24. Night- or shift-work sleep schedule.
25. Employment as a commercial driver or operator of heavy or hazardous equipment.
26. Smoking more than 10 cigarettes or 2 cigars per day.
27. Unwilling to use specified contraception.
28. Unwilling to limit alcohol consumption to no greater than 2 units/day or less, not to be consumed within 3 hours of bedtime.
29. Unwilling to limit caffeinated beverage intake (e.g., coffee, cola, tea) to 400 mg/day or less of caffeine, not to be used within 3 hours of bedtime.
30. Any condition that in the investigator's opinion would present an unreasonable risk to the participant, or which would interfere with their participation in the study or confound study interpretation.
31. Participant considered by the investigator, for any reason, an unsuitable candidate to receive AD036 or unable or unlikely to understand or comply with the dosing schedule or study evaluations.

5.3 Meals and Dietary Restrictions

1. Participants should refrain from consumption of any nutrients known to modulate CYP enzyme activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, pomegranate, and Seville or Moro [blood] orange products) within 72 hours before the first administration of study drug, during the study, and until final discharge.
2. Diet should be generally stable during the study, e.g., new diet programs should not be initiated.

5.4 Caffeine, Alcohol, and Tobacco

1. Participants should refrain from more than 2 units per day of alcohol, consumed no less than 3 hours prior to bedtime.
2. Moderate consumption of caffeinated beverages, containing up to a total of 400 mg caffeine per day, is permitted, consumed no less than 3 hours prior to bedtime.

5.5 Activity

There are no restrictions on physical activity during the study other than that physical activity should be generally stable during the study (e.g., new exercise programs should not be initiated).

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants that meets the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened, except if the opportunity for rescreening has been enabled by protocol amendment.

6 Study 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.

6.1 Study Treatment(s) Administered

Two different blinded capsules are taken each night of drug treatment, as arranged in blister packaging. On placebo nights, 2 placebo tablets will be taken. On nights of randomized study treatment, 1 capsule of atomoxetine and 1 capsule of oxybutynin, or of corresponding placebo, are taken approximately 30 minutes before the participant's planned bedtime.

Study Treatment Name:	**Atomoxetine hydrochloride**	**Oxybutynin chloride**
Dosage Formulation:	Capsule	Capsule
Dosage Level:	75 mg or 25 mg	5 mg or 1.5 mg
Route of Administration:	Oral	Oral
Dosing Instructions:	1 capsule will be administered daily with at least 20 mL water	1 capsule will be administered daily with at least 20 mL water
Storage/Packaging/Labeling:	Store per package insert. Study treatment will be provided in blister packaging. Each blister package will be labeled as required per country requirement.	Store per package insert. Study treatment will be provided in blister packaging. Each blister package will be labeled as required per country requirement.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatments and only authorized site staff may supply or administer study treatments. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. After receiving Sponsor approval in writing, PAREXEL is 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.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized using an Interactive Response Technology (IRT). Each participant will be assigned a unique number (randomization number) that encodes the participant's assignment to 1 of the 4 arms of the study, according to the randomization schedule generated by the Sponsor (or designee) using a validated computer program. Details of the procedure are described in the IRT Manual provided to all sites.

Study treatment will be dispensed the morning after PSG screening, as summarized in Section 1.3.

Returned study treatment should not be redispensed to the participants.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. If a participant's study treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Participants will be randomly assigned in a 1:1:1:1 equal allocation ratio to receive 1 of 3 different study treatment doses or placebo, using permuted blocked randomization. Investigators will remain blinded to each participant's assigned study treatment throughout the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4 Study Treatment Compliance

Participants will be required to return any unused study treatment capsules at Visit 4. Unused capsules will be counted and recorded by study personnel to assess study treatment compliance.

6.5 Concomitant Therapy

Concomitant therapy with the following medications is disallowed:

- MAOIs or other drugs that affect monoamine concentrations (e.g., rasagiline) [MAOIs are contraindicated for use with atomoxetine]
- Selective Serotonin Reuptake Inhibitors (e.g., paroxetine)
- Selective Norepinephrine Reuptake Inhibitors (e.g., duloxetine)
- Norepinephrine Reuptake Inhibitors (e.g., reboxetine)
- Alpha-1 antagonists (e.g., tamsulosin)
- Tricyclic antidepressants (e.g., desipramine)
- CYP2D6 inhibitors
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Benzodiazepines and other anxiolytics
- Opioids
- Sedatives other than nonbenzodiazepine "Z-drugs" (zolpidem, zaleplon, eszopiclone)
- Muscle relaxants
- Pressor agents
- Drugs with clinically significant cardiac QT-interval prolonging effects
- Drugs known to lower seizure threshold (e.g., chloroquine)
- Amphetamines
- Antiepileptics
- Antiemetics
- Modafinil or armodafinil
- $Beta_2$ agonists, (e.g., albuterol)
- Antipsychotics
- Anticholinergics and anticholinesterase inhibitors, including drugs with substantial anticholinergic side effects, (e.g., first generation antihistamines)
- Sedating antihistamines
- Pseudoephedrine, phenylephrine, oxymetazoline
- Nicotine replacement products

- Most drugs for Parkinson's, Alzheimer's, Huntington's, Amyotrophic Lateral Sclerosis, or drugs for other neurodegenerative diseases

Medications that do not have substantial effects on the central nervous system (CNS), respiration, or muscle activity are generally allowed if dose and frequency is stable for 3 months prior to enrollment and during the course of the study, including, but not necessarily limited to, the following drugs and drug classes:

- Antihypertensives (angiotensin-converting-enzyme/angiotensin II receptor blocker inhibitors, calcium channel blockers, spironolactone, hydrochlorothiazide, etc.)
- Statins
- Proton pump inhibitors and histamine h_2 receptor blockers
- Over-the-counter (OTC) antacids
- Non-sedating antihistamines (e.g., cetirizine, loratadine)
- Eszopiclone, zolpidem, or zaleplon
- Melatonin
- Non-steroidal anti-inflammatory drugs and acetaminophen
- Laxatives
- Erectile dysfunction drugs
- Inhaled corticosteroids (e.g., fluticasone)
- Antidiabetics
- Ocular hypotensives and other ophthalmics (e.g., timolol)
- Hormonal therapy (e.g., estrogen replacement or anti-estrogens) and hormonal contraceptives
- Thyroid medications
- Anticoagulants
- OTC topicals (e.g., topical pain relievers)
- Osteoporosis drugs

6.6 Dose Modification

Through protocol amendment, planned doses may be decreased on an individual or group basis according to emerging safety and tolerability data.

6.7 Treatment After the End of the Study

Not applicable. No subsequent open-label extension is planned following the study.
Study treatment will not be available after the end of study participation.

7 Discontinuation of Study Treatment and Participant Discontinuation

Refer to the SoA for data that are to be collected at the time of study discontinuation, during follow-up, and for any further evaluations that need to be completed.

7.1 Discontinuation of Study Treatment

If a clinically significant finding is identified, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an adverse event (AE).

7.2 Stopping Criteria

7.2.1 Individual Participant Stopping Criteria

- Incidents of abuse, diversion, or misuse of the study treatment.
- Incidents of clinical significance: hallucinations, amnesia, delusional thinking, delirium, manic symptoms, aggressive behavior, suicidality, homicidality, agitation, confusion, or convulsions/seizures.
- Participants reporting any SAE.
- Acute urinary obstruction.
- Any other AE that in the judgment of the Investigator necessitates the participant stopping to protect participant safety.

Participants discontinued from dosing will undergo end of study procedures with follow-up monitoring of the AE(s) as clinically indicated.

7.3 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- All participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.
- Participation may be terminated before completing the study and the reason recorded as follows:
    - Withdrawal due to AE
    - Withdrawal due to incident abuse, diversion, or misuse of the study treatment
    - Loss to follow-up
    - Participant withdrew consent at own request
    - Other

7.4 Loss of Participants to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record/eCRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.

- As protocol waivers or exemptions are not allowed with the exception of immediate safety concerns, these should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, excluding any extra assessments that may be required for safety or technical issues, will not exceed around 50 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, as per the Investigator or designee's discretion.

8.1 Efficacy Assessments

The Study Reference Manual provides detailed information for the various scales discussed in Section 8.1.1 through Section 8.1.6.

8.1.1 Efficacy Endpoint Scales

- The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in 8 different activities in recent times. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'. The questionnaire takes approximately 2 or 3 minutes to answer. The ESS is asked during screening as an enrollment criterion. The ESS is also used as a study efficacy outcome. The ESS is administered the day of the non-PSG screening and approximately the same time of day prior to PSG recordings.

- The Participant Global Impression of Severity (PGI-S) is a global index that may be used to rate the severity of a specific condition, (i.e., it is a single-state scale). The scale consists of a 1-item questionnaire designed to assess the participant's impression of disease severity. The scale is considered to have clinical relevance for the participant because it allows participants to respond based on factors that they judge to be the most important in their health status. The PGI-S is administered at the baseline/screening PSG Visit 2 and at PSG Visit 4. The PGI-S is administered at approximately the same time prior to each PSG recording.
- The Participant Global Satisfaction with Treatment scale consists of a 1-item questionnaire designed to assess the participant's satisfaction with the experimental treatment, considering both safety and efficacy. The scale is administered at the end of the study, at the EOS Visit.

8.1.2 Safety and Abuse Liability Scale

- The Cocaine Selective Severity Assessment **(**CSSA) was designed to measure cocaine withdrawal signs and symptoms during detoxification, and 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. The CSSA will be used in this study to identify psychiatric issues and to characterize the potential of the atomoxetine/oxybutynin combination to elicit withdrawal symptoms similar to those elicited by cocaine withdrawal. A modified version of the assessment will be used in this study to measure potential withdrawal signs and symptoms from the study treatment; "cocaine" will be replaced with "study drug". The scale is administered by clinical staff. A score of ≥3 on Item 17, or Investigator judgment that the patient is suicidal, will initiate further clinical evaluation and appropriate measures to protect participant safety. (Note: Questions 4 and 5 of the CSSA will not be asked at baseline).

8.1.3 Functional Endpoints

- The Digit Symbol Substitution Test (DSST) is a paper-and-pencil cognitive and psychomotor test that requires patients to identify and copy symbols that are matched to numbers according to an instruction key located at the top of the page. The DSST is commonly used to screen for impairment related to pharmaceuticals and is also sensitive to sleep restriction. The DSST is administered the morning after the inpatient PSG nights, at approximately the same time after awaking from each PSG.

- The Delayed Word Recall Test (DWRT) is a brief and efficient test of verbal learning and recent memory. The DWRT is administered the morning after the screening/baseline PSG (Visit 2) and in the morning after PSG Visit 4. The DWRT is administered at approximately the same time after awaking from each PSG.

8.1.4 Screening/Eligibility Scales

- The IPSS is typically used to diagnose benign prostatic hyperplasia and to monitor disease progression and response to therapy. The participant is asked to choose the rating that best represents their condition. The scale ranges from 1 to 5, with 5 representing the most symptomatic disease and giving an overall maximum possible score of 35. The IPSS is administered to males as an enrollment criterion.
- The STOP-Bang questionnaire has been developed and validated as a screening tool for OSA. The STOP-Bang questionnaire is used in the study only for participants who do not have a previous diagnosis of OSA or use of CPAP, to determine whether there is a high enough pre-test probability of moderate to severe OSA to conduct enrollment screening. The standard STOP-Bang scoring used in the sleep clinic has only moderate specificity. For the purposes of this study, scoring with higher specificity is used (STOP-Bang score ≥5, or STOP ≥ 2 + BMI >35 kg/m^2) to decrease screening participants who are unlikely to meet enrollment criteria.

8.1.5 Polysomnography

- Methods: Standard overnight PSG recording and data interpretation will be performed in accordance with the American Academy of Sleep Medicine (AASM) scoring manual. Participants will be instrumented with standard PSG electrodes. Time of lights out will be established according to the participants' habitual schedule and kept constant across the PSG study nights. The participants will be given 8 hours of time-in bed.
- Technically Adequate Test: The screening/baseline PSG study must meet the following criteria for participants to enroll:
    - At least 4 hours of sleep.
    - At least 2 electroencephalograms (EEGs) and 2 electrooculography traces for the full night.
    - P nasal for at least 60% of the night and thermistor or both respiratory belts signals for the full night for scoring respiratory events.

- At least 30% of sleep in supine position.

Participants who do not have a technically adequate test at baseline can be retested at the discretion of the investigator.

- Scoring: For uses other than study enrollment, all studies will be scored by centralized PSG technologists, blinded to treatment assignment. Baseline and on-treatment PSGs for each individual participant will be scored by the same technologist. Scoring will be conducted according to the American Academy of Sleep Medicine manual scoring criteria.

8.1.6 Home Oximetry

- Participants will be instructed on the at-home use of oximetry at Visit 2 and will be provided with an oximeter that is capable of nightly recording and storage of data for the entire at-home period (study Days 1-11). Participant use of oximeter will be reinforced during the study visit on Day 6 (Visit 3), and through a reminder telephone contact on Day 10. The study personnel will replace the batteries in the oximeter during the Day 6 study visit. The number per hour of oxygen desaturations ≥ 4% will be compared between the average of the baseline nights and the average of the randomized study treatment nights.

8.2 Safety Assessments

- Planned time points for all safety assessments are provided in the SoA.
- 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, as indicated by the initial data described above, 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 CNS effects such as memory difficulty. Safety monitoring will therefore include psychomotor vigilance testing and memory testing.

8.2.1 Physical Examinations

- Physical examinations at screening/baseline include anthropomorphic data relevant to OSA: neck circumference at superior border of cricothyroid cartilage; waist circumference at highest point of iliac crest; evaluation of the oropharynx, hypopharynx, and facial skeletal structure; Mallampati score; tonsils evaluation (0-3+); presence of micrognathia; nasal patency.
- The general physical examination at screening/baseline includes an assessment of general appearance and a review of physical systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems). Height and weight will also be measured and recorded (with shoes removed and wearing light indoor clothing).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Assessment of vital signs (seated blood pressure, pulse rate, body temperature, respiratory rate) will be performed at the time points indicated in the SoA (Section 1.3).
- Vital signs will be measured at all visits in a seated position after 5 minutes rest and will include temperature, respiratory rate, systolic and diastolic blood pressure, and pulse. Measurements should be made in the same arm of the participant at each visit.
- Systolic and diastolic blood pressure will be repeated for a total of 3 measurements, each at least 2 minutes apart.
- The method used to measure body temperature at screening should be maintained throughout the study for each participant, and should be indicated (e.g., ear, mouth, armpit).

8.2.3 Electrocardiograms

- A 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures the PR, QRS, and QT intervals, and the corrected QT-interval (QTc). The ECG will be recorded in the semi-supine position after the participant has rested in this position for at least 10 minutes.

8.2.4 Clinical Safety Laboratory Assessments

- Refer to Appendix 10.2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically relevant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from laboratory assessments not specified in the protocol and performed at the institution’s local laboratory result in the need for a change in participant management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded in the eCRF.

8.2.5 Suicide Risk Monitoring

Atomoxetine and oxybutynin are CNS-active drugs. There has been concern that some CNS-active drugs may be associated with an increased risk of suicidal ideation or behavior when given to participants with certain conditions or baseline characteristics. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to adults, it is important to monitor for such events during this clinical study.

Suicidal ideation in children and adolescents is a boxed warning for atomoxetine; however, analysis in adult participants, the target population for the proposed OSA study, did not reveal an increased risk of suicidal ideation or behavior in association with atomoxetine.

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 and will initiate further clinical evaluation and appropriate measures to protect participant safety. Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing participants who experience signs of suicidal ideation or behavior. Families and caregivers of participants should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

8.3 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study and/or study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of informed consent form (ICF) until Visit 5/EOS at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably

related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification (within 24 hours, see Appendix 3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- 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.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

If a female partner of a male study participant who has been exposed to the study treatment becomes pregnant, the pregnancy and outcome of pregnancy should be monitored.

8.4 Treatment of Overdose

For this study, any dose of atomoxetine greater than 75 mg and of oxybutynin greater than 5 mg more frequently than QHS will be considered an overdose.

In the event of an overdose, the Investigator should refer to the approved product label for advice on overdose and:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until atomoxetine hydrochloride and/or oxybutynin chloride can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case by case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Genetics

A genetic sample will be taken during Treatment Period 1 only, on the screening/baseline visit (prior to randomization) to test for CYP2D6 poor metabolizers.

9 Statistical Considerations

9.1 Statistical Hypotheses

The null hypothesis is no change in the proportion of participants with ≥50% improvement in AHI from baseline to the second PSG visit (Visit 4) in the 75 mg/5 mg dose group compared with placebo.

9.2 Sample Size Determination

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, 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.

9.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who signed the ICF (including screening failures).
Modified Intent to Treat (mITT) Population	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. Participants will be analyzed for efficacy according to the treatment group into which they are randomized.
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 for safety based on the treatment received. A precise definition of "as actually received" will be added in the Statistical Analysis Plan (SAP).
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.

The primary endpoint comparison between the high dose (75/5) and placebo will consider all mITT participants randomized to those 2 groups; participants not returning for their second PSG night will be considered treatment non-responders.

9.4 Primary and Secondary Analyses

The SAP will be developed and finalized prior to database lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints. Further details are presented in the SAP.

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. OSA is often more severe in the supine sleeping position, and variability in time spent in the supine position between baseline and during on-drug PSG tests can otherwise introduce variability.
- 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 ESS from baseline to the second PSG visit in the 75/5 dose group compared with placebo.
- Change from baseline in the 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 compared with the lower treatment dose of 75/1.5.

9.5 Interim Analyses

No formal interim analysis is planned.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
    - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.

    - Applicable laws and regulations.

- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
    - Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC guidelines, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the participant or the participant's legally authorized representative.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

When the clinical study report is completed, the Sponsor will provide the major findings of the study to the Investigator. A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinTrials.gov). The results may also be submitted for publication.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will lock the database.

- The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.11.1.

10.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

10.1.9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the US Investigational New Drug (IND) under which the study is being conducted.

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.11.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC/eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The EDC/eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the EDC/eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures PAREXEL and the Sponsor of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Laboratory testing is performed non-fasting.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 2: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Platelet Count RBC Count	<u>RBC Indices:</u> MCV MCH %Reticulocytes	<u>WBC count with Differential:</u> Basophils Eosinophils Lymphocytes Neutrophils Monocytes
Serum Chemistry	Albumin BUN Creatinine Potassium Sodium Total and direct bilirubin Total Protein Uric acid	ALT AST Alkaline phosphatase Calcium γGTP Glucose Total cholesterol Chloride Bicarbonate	
Routine Urinalysis	Specific gravity pH, protein (albumin), glucose, ketones, blood (RBC), WBC by dipstick Microscopic examination (if blood or protein is abnormal)		
Other Tests	• HbA1c (Screening Visit only) • CYP2D6 genotype • Serum hCG pregnancy test at screening and urine hCG tests at baseline. Additional testing may be performed if needed in WOCBP. • Alcohol and drugs of abuse screening		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CYP2D6 = cytochrome P450 2D6; γ-GTP = gamma guanosine-5'-triphosphate; HbA1c = hemoglobin A1c (glycated hemoglobin); hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell count; WBC= white blood cell; WOCBP = women of childbearing potential.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• 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. • NOTE: 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.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the PAREXEL Clinical Studies Safety Center. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the PAREXEL Clinical Studies Safety Center. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of 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.

Assessment of Causality

- 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 Clinical Studies Safety Center. 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 PAREXEL Clinical Studies Safety Center.**
- 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.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by PAREXEL Clinical Studies Safety Center to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide PAREXEL with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to PAREXEL Clinical Studies Safety Center within 24 hours of receipt of the information.

Reporting of SAE to PAREXEL Clinical Studies Safety Center

SAE Reporting to PAREXEL Clinical Studies Safety Center Via EDC Tool

- The Investigator must report any SAEs to the PAREXEL Clinical Studies Safety Center within 24 hours of becoming aware of the event.
- When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.
- The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/PAREXEL will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents (Investigator's Brochure or US product labeling for atomoxetine or oxybutynin). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or by telephone.
- Contacts for SAE reporting can be found in the Study Reference Manual.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
Any AE that is serious, associated with the use of the study treatment, and unexpected (SUSAR) has additional reporting requirements, as described below. • If the SUSAR is fatal or life-threatening, associated with study treatment, and unexpected, regulatory authorities and IECs will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total). • If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study treatment, and unexpected, regulatory authorities and IECs will be notified within 15 calendar days after the Sponsor learns of the event. The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of participants. Follow-up information may be submitted if necessary. The Sponsor will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

Reporting Serious Adverse Events

The Investigator must report any SAEs to the PAREXEL Clinical Studies Safety Center within 24 hours of becoming aware of the event.

When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/PAREXEL will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents (Investigator's Brochure or US product labeling for atomoxetine or oxybutynin). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from signing of informed consent until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator

must be reported only if they are considered (in the opinion of the Investigator) causally-related to study treatment.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

PAREXEL International Corporation
Clinical Studies Safety Center

The names and contact information for SAE reporting
will be provided in the Study Reference Manual.

1. Telephone the Medical Monitor/Drug Safety Specialist to inform him/her that you are faxing an SAE form. If the Medical Monitor is not available or you are calling after business hours (8:30 am to 5:30 pm Eastern time, Monday to Friday), leave a message in his/her voice mailbox.

2. Provide the Medical Monitor with the Principal Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

3. Fax the completed SAE form and any supporting documentation within 24 hours of becoming aware of the event to the email address or fax number listed on the SAE reporting form (investigator site file).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

WOCBP

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy

- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

NOTE: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Post-menopausal female
    - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

Contraception Guidance:

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if the agree to ONE of the following during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study treatment.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or to use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods That Are User Dependent[1] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent[1]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

1 Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- An additional serum pregnancy testing should be performed at Visit 5 (EOS).
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect any follow up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported, regardless of fetal state (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: List of Abbreviations

AHI	apnea-hypopnea index
AE	adverse event
Bang	Body mass index, Age, Neck circumference, and Gender criteria
BMI	body mass index
CFR	Code of Federal Regulations
CNS	central nervous system
CPAP	continuous positive air pressure
CSSA	Cocaine Selective Severity Assessment
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
EEG	electroencephalogram
eCRF	electronic case report form(s)
EDC	electronic data capture
EMG_{gg}	genioglossal electromyographic
EOS	end of study
ESS	Epworth Sleepiness Scale
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
OSA	obstructive sleep apnea
OTC	over-the-counter
MAOI	monoamine oxidase inhibitor
NREM	non-rapid eye movement
PGI-S	Participant Global Impression of Severity

PK	pharmacokinetic(s)
PSG	polysomnography
DWRT	Delayed Word Recall Test
QHS	1 dose every night at bedtime
REM	rapid eye movement
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
STOP	Snoring, Tiredness, Observed apnea, and Blood pressure criteria
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential

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Declaration of the Investigator

Title: 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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, EDC system/eCRF, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number