Apnimed, Inc.
20 Holyoke Street
Cambridge, MA 02138
info@apnimed.com

October 18, 2022

To: ClinicalTrials.gov

This is a cover page to the redacted clinical protocol for APC-003 titled Phase 2 Double-Blind Placebo-Controlled 4-Period Single-Dose Crossover Factorial Study to Evaluate the Contribution of the Individual Drug Components to the Efficacy of the Combination of Atomoxetine and R-oxybutynin in Obstructive Sleep Apnea.

The APC-003 clinical protocol is associated with NCT04580394.

The following proprietary information was redacted from the clinical protocol for APC-003:

- IND number

Sincerely,

DocuSigned by:
Jeanne Brittain
Signer Name: Jeanne Brittain
Signing Reason: I approve this document
Signing Time: 10/18/2022 | 2:12:35 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: 10/19/2022 | 8:31:01 AM EDT 35E78DD6A7F34F8AA557BB15D08339BC	10/19/2022

Title Page

Protocol Title: Phase 2 Randomized Double-Blind Placebo-Controlled 4-Period Single-Dose Crossover Factorial Study to Evaluate the Contribution of the Individual Drug Components to the Efficacy of the Combination of Atomoxetine and R-oxybutynin in Obstructive Sleep Apnea

Protocol Number: APC-003

Version Number: 2.0

Compound Number: AD109

Short Title: AD109 Factorial Study

Sponsor Name and Legal Registered Address:

Apnimed, Inc.

20 Holyoke Street

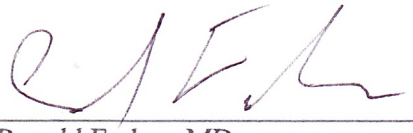
Cambridge, MA 02138

Regulatory Agency Identifying Number: IND 141505

Approval Date: 6 January 2021

Date and Version of Previous Protocol: 6 October 2020, Version 1.3

Sponsor Signatory:



15 Jan 2021

Ronald Farkas, MD
Chief Medical Officer

Date

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Phase 2 Randomized Double-Blind Placebo-Controlled 4-Period Single-Dose Crossover Factorial Study to Evaluate the Contribution of the Individual Drug Components to the Efficacy of the Combination of Atomoxetine and R-oxybutynin in Obstructive Sleep Apnea

Sponsor Study No.: APC-003

Phase: 2

Sponsor: Apnimed, Inc.

Rationale:

Previous studies conducted by the sponsor (under IND 136752) and academic investigators indicate that the combination drug composed of atomoxetine and oxybutynin (designated AD036) is effective for the treatment of obstructive sleep apnea (OSA). Oxybutynin is a racemic mixture of R and S enantiomers. Oxybutynin is approved in the U.S. for overactive bladder. Efficacy of oxybutynin in overactive bladder may result both from antimuscarinic effects and smooth muscle spasmolytic effects. The contribution to efficacy of oxybutynin in OSA is believed to be related to the antimuscarinic effects, whereas spasmolytic effects may lead to effects on the bladder that are undesirable in typical OSA patients. The R-enantiomer of oxybutynin has been shown to confer the antimuscarinic effect of oxybutynin, whereas the spasmolytic effects (and other effects on calcium channel antagonism and local anesthetic effects) are non-stereoselective properties of both the enantiomers. Apnimed therefore believes that the combination of the R-enantiomer of oxybutynin with atomoxetine, designated AD109, may have an improved safety and efficacy profile in OSA compared to the combination with the racemate of oxybutynin.

This factorial study is designed to demonstrate that both atomoxetine and R-oxybutynin contribute to the efficacy of AD109 in OSA, and thus to fulfill FDA requirements for approval of combination drugs under 21 CFR Subpart B Section 300.50 Fixed-combination prescription drugs for humans.

Overall Design:

Study APC-003 is a randomized, double blind, placebo-controlled, 4-period, single-dose crossover factorial study in patients with OSA. A screening visit and polysomnographic (PSG) exam will be conducted to establish that each participant meets study enrollment criteria. Each participant will then receive a single dose of each of the following during 4 overnight PSG exams, each separated by a one week washout period:

- Atomoxetine 75 mg + R-oxybutynin 2.5 mg (AD109)
- Atomoxetine 75 mg
- R-oxybutynin 2.5 mg
- Placebo

The primary hypothesis of the crossover study is that AD109 is superior to each of the other 3 arms, on the endpoint of Hypoxic Burden (HB), a measure of the depth and duration of the ventilatory disturbance in OSA.

Number of Participants:

A total of 58 participants will be enrolled.

Study Duration:

The overall study duration will be up to 14 weeks, as follows:

- Screening, up to 4 weeks;
- 4-period crossover, up to 8 weeks;
- End of Study Evaluation, 2 weeks post crossover period

1.2 Schedule of Activities (SoA)

Table 1 Schedule of Activities

Procedures	Screening		4-Way Crossover Period Visit 3-6								End of Study Evaluation[1]
	Daytime V1	PSG V2	PSG V3	Wash-out [2]	PSG V4	Wash-out	PSG V5	Wash-out	PSG V6	Wash-out	
Trial Day (Visit Window)	**Up to 4 weeks**		**Up to 8 weeks**								2 weeks post V6 ± 3 days
Informed consent	X										
Non-PSG enrollment criteria	X										
Demography	X										
ESS	X										
Physical exam	X										
Medical history	X										
Clinical laboratory test	X										
Pregnancy test[3]	X										
12 Lead ECG	X										
PSG Exam		X[4]	X		X		X		X		
Randomization[5]			X								
Administration of study treatment[6]			X		X		X		X		
DSST[7]			X		X		X		X		
Vital signs[8]	X	X	X		X		X		X		
AE/SAE monitoring			X	X	X	X	X	X	X	X	X
Prior/concomitant medication monitoring	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; PSG = polysomnography; SAE = serious adverse event; WOCBP = women of childbearing potential.

[1] Can be conducted remotely. For patients enrolling in Study APC-003-OLE, can be conducted concurrently with first visit of Study APC-003-OLE.
[2] Each washout period is a minimum of 7 days
[3] WOCBP only
[4] A PSG conducted by the study site within 6 months that meets PSG enrollment criteria can take the place of a screening PSG and V2
[5] Randomization occurs when participant meets enrollment criteria up to the time of the first crossover period
[6] Study medication administered immediately before lights out
[7] Administer at similar time after awakening after each crossover PSG, approximately 1 hour after awakening
[8] Vital signs include the following: seated blood pressure, pulse, respiratory rate; vital signs on PSG nights taken after admission to PSG lab

2 Introduction

2.1 Study Rationale

Previous studies conducted by the sponsor (under IND 136752) and academic investigators indicate that the combination drug composed of atomoxetine and oxybutynin (designated AD036) is effective for the treatment of obstructive sleep apnea (OSA). Oxybutynin is a racemic mixture of R and S enantiomers. Oxybutynin is approved in the U.S. for overactive bladder. Efficacy in overactive bladder may result both from antimuscarinic effects of oxybutynin and smooth muscle spasmolytic effects. The contribution to efficacy of oxybutynin in OSA is believed to be related to antimuscarinic effects, whereas spasmolytic effects may lead to effects on the bladder that are undesirable in typical OSA patients. The R-enantiomer of oxybutynin has been shown to confer the antimuscarinic effect of oxybutynin, whereas the spasmolytic effects (and other effects on calcium channel antagonism and local anesthetic effects) are non-stereoselective properties of both the enantiomers. Apnimed therefore believes that the combination of the R-enantiomer of oxybutynin with atomoxetine, designated AD109, may have an improved safety and efficacy profile in OSA compared to the combination with the racemate of oxybutynin.

This factorial study is designed to demonstrate that both atomoxetine and R-oxybutynin contribute to the efficacy of AD109 in OSA, and thus to fulfill FDA requirements for approval of combination drugs under 21 CFR Subpart B Section 300.50 Fixed-combination prescription drugs for humans.

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

AD109 is a new fixed dose drug combination of atomoxetine and R-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. R-oxybutynin has never been marketed, but racemic oxybutynin is approved as 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 oxybutynin in overactive bladder may result both from antimuscarinic effects of oxybutynin and smooth muscle spasmolytic effects. The contribution to efficacy of oxybutynin in OSA is believed to be related to antimuscarinic effects, whereas spasmolytic effects may lead to effects on the bladder that are undesirable in typical OSA patients. The R-enantiomer of oxybutynin has been shown to confer the antimuscarinic effect of oxybutynin, whereas the spasmolytic effects (and other effects on calcium channel antagonism and local anesthetic effects) are non-stereoselective properties of both the enantiomers. Apnimed therefore believes that the combination of the R-enantiomer of oxybutynin with atomoxetine may have an improved safety and efficacy profile in OSA compared to the combination with the racemate of oxybutynin. This factorial study, APC-003, is designed to demonstrate that both atomoxetine and R-oxybutynin contribute to the efficacy of AD109 in OSA.

3 Endpoints

	Endpoints
Primary	• Change in Hypoxic Burden (HB) 4%, (scored in reference to AHI 4%), AD109 vs. other 3 study treatments
Secondary	• Change in Apnea Hypopnea Index (AHI) 4% • Change in Oxygen Desaturation Index (ODI) • Total time with SaO_2 <90%, PSG nights • Proportion of participants with ≥50% reduction, AHI, HB and ODI
Exploratory	• PSG sleep and arousal parameters • PSG respiratory parameters
Safety Endpoints	• Physical exam, vital signs, clinical laboratory assessment • Spontaneous adverse events, including the post-dosing period • DSST • PSG parameters: heart rate, ECG, EEG, oximetry
Abbreviations: AHI = apnea-hypopnea index; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EEG = electroencephalogram; HB = Hypoxic Burden; ODI = Oxygen Desaturation Index; OSA = obstructive sleep apnea; PSG = polysomnography; SaO_2 = oxygen saturation.	

4 Study Design

4.1 Overall Design

Study APC-003 is a double-blind, placebo-controlled 4-period single dose crossover study designed to demonstrate the individual contribution of atomoxetine and R-oxybutynin to the efficacy of AD109.

Participants will undergo initial pre-screening to determine potential study eligibility. Patients selected for further screening should either have a previous history of OSA of a severity consistent with enrollment criteria or be at high risk (e.g. as assessed by STOP-Bang Questionnaire score). Only patients who meet all non-PSG enrollment criteria at Visit 1 are eligible for a screening PSG. A prior full-night PSG conducted by the study site within 6 months of Visit 1 that meets PSG enrollment criteria can take the place of a screening PSG.

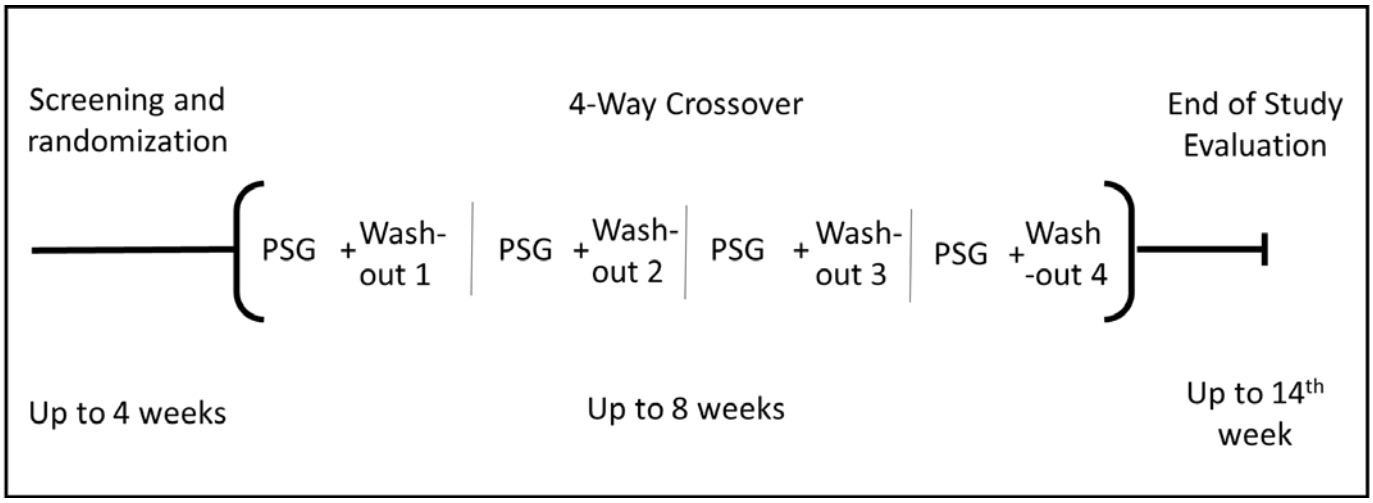
Patients who meet all enrollment criteria will be randomized to receive the following experimental treatments, one treatment on each of 4 PSG night:

- Atomoxetine 75 mg + R-oxybutynin 2.5 mg (AD109)
- Atomoxetine 75 mg
- R-oxybutynin 2.5 mg
- Placebo

Dosing of the study treatment will occur immediately prior to lights out. Each morning following PSG exams in the crossover period the DSST will be administered.

Each PSG night is followed by a 1-week washout period. AE/SAE information is recorded at each study visit and by telephone contact with participants during each washout period and at the end of the final washout period. Overall study duration will be up to 14 weeks. A total of 58 participants will be enrolled. Participants who withdraw from the study will not be replaced.

Figure 1: Overview of Study Design



PSG = polysomnography.

4.2 Scientific Rationale for Study Design and Dose

Previous Phase 2 studies conducted by Apnimed and academic collaborators support that the combination of atomoxetine and racemic oxybutynin is effective for OSA, and that both drug components are necessary for this efficacy. This factorial study is designed to demonstrate that both atomoxetine and R-oxybutynin contribute to the efficacy of AD109 in OSA. The dose of atomoxetine has been used in previous Phase 2 studies supporting efficacy and safety for OSA in combination with 5 mg racemic oxybutynin. Because the R-enantiomer of oxybutynin confers about 2-fold the anticholinergic activity of the racemate, with such activity thought to be the major contributor to efficacy in OSA, the dose of R-oxybutynin was reduced to 2.5 mg.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AD109 is provided in the Investigator's Brochure.

4.3 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study through 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

Eligible participants will be recruited both from the existing clinic population at the study sites, including databases of previous subjects who participated in other studies, and through direct advertising to the community.

Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Age and Sex

1. Between 25 to 65 years of age, inclusive, at the Screening Visit.

Objective Disease Measures

2. AHI 10 to <45, or AHI ≥45 if any one of the following criteria are met:
   a. Fraction of hypopneas ($F_{hypopnea}$) is >90% or
   b. Mean oxygen desaturation of obstructive events is ≤4% or
   c. Fraction of hypopneas is 50-90% and mean oxygen desaturation is 4-8%

   Note: Hypopneas defined by 4% oxygen desaturation

Weight

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

Male participants:

4. 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:

5. 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.
6. 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

7. 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.
8. 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 (combination medications count as 1 medication).
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, urinary retention or insomnia.
8. Medically unexplained positive screen for drugs of abuse (excluding THC/marijuana) or history of 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 as determined by investigator.
10. Clinically significant cognitive dysfunction as determined by investigator.
11. Untreated narrow angle glaucoma.
12. Women who are pregnant or nursing.

Prior/Concomitant Therapy

13. CPAP should not be used for at least 2 weeks prior to first study PSG and throughout the study.

14. 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.
15. 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.
16. History of oxygen therapy.
17. Use of medications from the list of disallowed concomitant medications.
18. 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

19. Use of another investigational agent within 30 days or 5 half-lives, whichever is longer, prior to dosing.

Diagnostic Assessments

20. ESS total score > 18.
21. Hepatic transaminases >2X the upper limit of normal (ULN), total bilirubin >1.5X ULN (unless confirmed Gilbert syndrome), estimated glomerular filtration rate < 60 ml/min.

Other Exclusions

22. <5 hours typical sleep duration.
23. Night- or shift-work sleep schedule which causes the major sleep period to be during the day.
24. Employment as a commercial driver or operator of heavy or hazardous equipment.
25. Smoking more than 10 cigarettes or 2 cigars per day, or inability to abstain from smoking during overnight PSG visits.
26. Unwilling to use specified contraception.
27. Unwilling to limit during the study period alcohol consumption to no greater than 2 standard units/day for men or 1 units/day for women, not to be consumed within 3 hours of bedtime.

28. Unwilling to limit during the study period 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.
29. 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.
30. Participant considered by the investigator, for any reason, an unsuitable candidate to receive AD109 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. During the outpatient portions of the study, participants should refrain from more than 2 standard units per day for men or 1 unit/day for women of alcohol, consumed no less than 3 hours prior to bedtime. Alcohol should not be consumed on PSG nights.
2. Moderate consumption of caffeinated beverages, containing up to a total of 400 mg caffeine per day, is permitted during the study period, 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 capsules are taken each night of drug treatment, either:

- 1 capsule of atomoxetine 75 mg + 1 capsule of R-oxybutynin 2.5 mg
- 1 capsule of atomoxetine 75 mg and 1 capsule of placebo
- 1 capsule of R-oxybutynin 2.5 mg and 1 capsule of placebo
- 2 capsules of placebo

Study medication is taken immediately prior to lights out.

Study Treatment Name:	**Atomoxetine hydrochloride or Placebo**	**R-Oxybutynin chloride or Placebo**
Dosage Formulation:	Opaque White Capsule, size 1 (about 0.75” length)	Opaque White Capsule, size 4 (about 0.5” length)
Dosage Level:	75 mg or placebo	2.5 mg or placebo
Route of Administration:	Oral	Oral
Dosing Instructions:	1 capsule administered with up to 240 mL water	1 capsule administered with up to 240 mL water
Storage/Packaging/Labeling:	Store at room temperature, in HDPE bottles	Store at room temperature in HDPE bottles

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

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized for the crossover phase of the study. Each participant will be assigned a unique number (randomization number) that encodes the participant's assignment to 1 of the sequences of the study, according to the randomization schedule using a validated computer program.

Returned study treatment should not be redispensed to the participants.

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.

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 Concomitant Therapy

Concomitant therapy with the medications listed below is disallowed. For medication that is typically used as-needed for symptomatic conditions (e.g. occasional use of a sleep aid), the

medication should not be used for at least one week prior to the first study PSG and for the duration of the study.

- 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 including 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 1 month prior to enrollment, 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)
- 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

6.5 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).

6.6 Stopping Criteria

6.6.1 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 considered possibly related or related to study treatment.
- 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.

6.7 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

6.8 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.

7 Study Assessments and Procedures

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

7.1.1 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.
- Scoring: All PSG studies (including screening PSG) will be scored by centralized PSG technologists, blinded to treatment assignment. Scoring will be conducted according to the American Academy of Sleep Medicine manual scoring criteria.

7.2 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 and 2 safety data for the combination. Safety assessments will include physical examinations, measurement of vital signs, monitoring and recording of AEs, SAEs, and pregnancies, recording of study or treatment discontinuations. 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. Daytime sleepiness is both a potential safety outcome and efficacy outcome in OSA. Both atomoxetine and oxybutynin may be associated with somnolence, and oxybutynin is additionally associated with anticholinergic CNS effects such as memory difficulty.

7.2.1 Physical Examinations

- The general physical examination at screening 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.

7.2.2 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.
- 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).

7.2.3 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. The ECG will be recorded in the semi-supine position after the participant has rested in this position for at least 10 minutes.

7.2.4 Clinical Safety Laboratory Assessments

- Refer to Section 9.2 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 and document this review. The laboratory reports must be filed with the source documents.
- All protocol-required laboratory assessments 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.

7.3 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.

7.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time of randomization until the end of the study at the timepoints specified in the SoA.

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.

7.3.2 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.

7.3.3 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. Further information on follow-up procedures is given in Appendix 3.

7.3.4 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.

7.3.5 Pregnancy

- Details of all pregnancies in female 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.

7.4 Treatment of Overdose

For this study, any dose of atomoxetine greater than 75 mg and of R-oxybutynin greater than 2.5 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 R-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.

7.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8 Statistical Considerations

8.1 Sample Size Determination

A total of 58 patients will enter the 4-treatment crossover study. The study will have 80% power to detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments on HB is at least -3.7 %min/h. This assumes that the within-subject standard deviation is 9, estimated from Study APN-006, and that the discontinuation rate is less than 20%.

8.2 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 randomly assigned treatment for each period.
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 for each period. 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. Participants in this population will be analyzed according to the treatment they actually received for each period. Treatment received is defined as the actual treatment taken during each period

8.3 Interim Analyses

No interim analysis is planned.

9 Supporting Documentation and Operational Considerations

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

9.1.1 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.

9.1.2 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.

9.1.3 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.

9.1.4 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.

9.1.5 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.

9.1.6 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.

9.1.7 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.

9.1.8 Publication Policy

- The Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The Sponsor retains the right to disapprove any submission for publication, including any publication using trial data, including abstracts, presentations or manuscripts.
- A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinTrials.gov).

9.1.9 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.

9.1.10 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.

9.1.10.1 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 the CRO and the Sponsor of the necessary support at all times.

9.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory.
- 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, MCHC)	WBC count with Differential
Serum Chemistry	Albumin BUN Creatinine Potassium Sodium Bilirubin Total Protein Uric acid	ALT AST Alkaline phosphatase Calcium Glucose Total cholesterol Chloride Bicarbonate	
Routine Urinalysis	Specific gravity, bilirubin, color, appearance, leukocyte esterase, nitrite, pH, protein (albumin), glucose, ketones, occult blood, urobilinogen Microscopic examination (if positive protein, leukocyte esterase, blood or nitrite)		
Other Tests	• HbA1c (Screening Visit only) • Serum hCG pregnancy test at screening. Additional testing may be performed if needed in WOCBP. • Urine test of drugs of abuse (marijuana, cocaine, amphetamine, methamphetamine, opiates, phencyclidine)		

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

Investigators must document their review of each laboratory safety report.

9.3 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 CRO. 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 CRO. • 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 CRO. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO.** • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 the CRO 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, the Investigator will provide the CRO 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 the CRO within 24 hours of receipt of the information.

Reporting of SAE to CRO

SAE Reporting to CRO Via EDC Tool
• The Investigator must report any SAEs to the CRO 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/CRO 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 or by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

All SAEs will be recorded from time of randomization 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.

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 CRO 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/CRO 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.

9.4 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:

- 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:

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. 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.

9.5 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
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
EOS	end of study
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HB	Hypoxic burden
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
PK	pharmacokinetic(s)
PSG	polysomnography
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

10 References

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Declaration of the Investigator

Title: Phase 2 Randomized Double-Blind Placebo-Controlled 4-Period Single-Dose Crossover Factorial Study to Evaluate the Contribution of the Individual Drug Components to the Efficacy of the Combination of Atomoxetine and R-oxybutynin in 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