# Title Page

**Protocol Title:** Phase 2 Randomized Double-Blind Placebo-Controlled Parallel-Arm Dose Finding Study to Compare Fixed Dose Combinations of Atomoxetine/Aroxybutynin (AD109) and Atomoxetine/Trazodone (AD504) to Atomoxetine alone or Placebo in Obstructive Sleep Apnea

**Protocol Name/Number:** MARIPOSA/APC-005

**Version Number:** 2.0

**Compound Number:** AD109 (Atomoxetine/Aroxybutynin); AD504 (Atomoxetine/Trazodone)

**Short Title:** MARIPOSA: ***M***easuring ***A***tomoxetine **R**x ***I***n ***P***atients with ***OSA***

**Sponsor Name and Legal Registered Address:**

Apnimed, Inc.

20 Holyoke Street

Cambridge, MA 02138

**Regulatory Agency Identifying Number:** IND 141505

**Approval Date:** 15 September 2021

**Date and Version of Previous Protocol:** 18 June 2021

**Sponsor Signatory:**

Ronald Farkas, MD
Chief Medical Officer

15 Sept 2021
Date

Updated as of June 1, 2026

# MARIPOSA/APC-005 Summary of Protocol Changes

| Version # | Version Date | Summary of Changes | Rationale (numbers correspond to change specified) | Submitted to FDA? | If Yes, Date | SAP Update Needed? | If Yes, Complete? |
|---|---|---|---|---|---|---|---|
| 1.0 | | Original | | | | | |
| 2.0 | 09/08/21 | Section 1.1<br>1. Addition of Atomoxetine/Trazodone (AD504) study arms. Removal of Atomoxetine 37.5mg/aroxybutynin 2.5mg arm for a total of 8 study arms<br>2. Increased 'n' to 280<br>3. Adjustment to randomization ratio<br>Section 2.1 | Section 1.1<br>1. Refined study design | | | | |

# Table of Contents

# 1 Protocol Summary

## 1.1 Synopsis

**Protocol Title:** Phase 2 Randomized Double-Blind Placebo-Controlled Parallel-Arm Dose Finding Study to Compare Fixed Dose Combinations of Atomoxetine/Aroxybutynin (AD109) and Atomoxetine/Trazodone (AD504) to Atomoxetine alone or Placebo in Obstructive Sleep Apnea

**Protocol Name/Number:** MARIPOSA/APC-005

**Phase:** 2

**Sponsor:** Apnimed, Inc.

**Rationale:**

Previous studies conducted by the sponsor and academic investigators indicate that the combination drug composed of atomoxetine with either aroxybutynin (designated AD109) or with trazodone (designated AD504) is effective for the treatment of obstructive sleep apnea (OSA). The present study is designed to advance dose-finding for AD109 and AD504 over a longer 1-month period of dosing.

**Overall Design:**

The MARIPOSA Study (APC-005) is a randomized, double blind, placebo-controlled, parallel-arm 1-month study in participants with OSA. A screening visit and two polysomnograms (PSGs) will be conducted to establish that each participant meets study enrollment criteria. The screening PSGs will serve as the baseline for the PSGs conducted during the 3$^{rd}$ and 4$^{th}$ weeks of drug treatment.

Enrolled participants will be randomized to one of 8 parallel treatment arms. The first week of dosing will be with a lower dose run-in or corresponding single-drug component or placebo, followed by the full dose taken in weeks 2-4. Note that study drug for arms 1-4 is provided as a single tablet taken nightly immediately before lights out, whereas study drug for arms 5-8 is composed one tablet and one capsule, **both** to be taken nightly immediately before lights out :

1. **Atomoxetine 75 mg/aroxybutynin 5 mg tablet (n = 40)**
    - Week 1: atomoxetine 37.5 mg/aroxybutynin 2.5 mg tablet
    - Weeks 2-4: atomoxetine 75/aroxybutynin 5 mg tablet

2. **Atomoxetine 75 mg/aroxybutynin 2.5 mg tablet (n = 40)**
    - Week 1: atomoxetine 37.5/aroxybutynin 2.5 mg tablet
    - Weeks 2-4: atomoxetine 75 mg/aroxybutynin 2.5 mg tablet
3. **Atomoxetine 75 mg tablet (n = 30)**
    - Week 1: atomoxetine 37.5 mg/placebo tablet
    - Weeks 2-4: atomoxetine 75 mg/placebo tablet
4. **Placebo tablet (n = 30)**
    - Week 1: placebo tablet
    - Weeks 2-4: placebo tablet
5. **Atomoxetine 75 mg tablet + Placebo capsule (n = 30)**
    - Week 1: atomoxetine 37.5 mg tablet + placebo capsule
    - Weeks 2-4: atomoxetine 75 mg tablet + placebo capsule
6. **Placebo tablet + placebo capsule (n = 30)**
    - Week 1: placebo tablet + placebo capsule
    - Weeks 2-4: placebo tablet + placebo capsule
7. **Atomoxetine 75 mg tablet + trazodone 100 mg capsule (n = 40)**
    - Week 1: atomoxetine 37.5 mg tablet + trazodone 50 mg capsule
    - Weeks 2-4: atomoxetine 75 mg tablet + trazodone 100 mg capsule
8. **Atomoxetine 75 mg tablet + trazodone 50 mg capsule (n = 40)**
    - Week 1: atomoxetine 37.5 mg tablet + trazodone 50 mg capsule
    - Weeks 2-4: atomoxetine 75 mg tablet + trazodone 50 mg capsule

The primary endpoint is the effect of the combined arms (n = 80) of atomoxetine 75 mg/aroxybutynin 2.5 mg (n = 40) and atomoxetine 75 mg/aroxybutynin 5 mg (n = 40) vs. combined placebo arms (n = 60) on the endpoint of Apnea Hypopnea Index 4% (AHI4).

**Number of Participants:**

A total of 280 participants will be enrolled in the ratio indicated above (4 / 4 / 3 / 3 / 3 / 3 / 4 / 4).

**Study Duration:**

The overall study duration for each participant will be up to 10 weeks, as follows:

- Screening, up to 4 weeks;
- Randomized treatment, 4 weeks (1st week low-dose run-in or corresponding placebo)
- End of Study Evaluation, 2 weeks post end of randomized treatment

## 1.2 Schedule of Activities (SoA)

**Table 1 Schedule of Activities**

| Procedures | Screening[1] and Baseline PSG[2] | | | Treatment Period | | | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | PSG V2 | PSG V3 | QHS Run-in dose | | QHS Full-dose | | | | V7 |
| | | | | At-home dosing | Clinic V4 | At-home dosing | PSG V5 | At-home dosing | PSG V6 | |
| **Trial Day/Duration** | **Up to 4 weeks** | | | **Day 1-7 ± 2** | **Day 7 ± 2** | **Day 8-21 ± 2** | **Day 21 ± 2** | **Day 22-28 ± 2** | **Day 28 ± 2** | **Day 42± 2** |
| Informed consent | X | | | | | | | | | |
| Enrollment criteria | X | X | X[3] | | | | | | | |
| Clinical lab test | X | | | | | | | | X[4] | |
| Pregnancy test[5] | X | | | | | | | | | |
| PSG | | X | X | | | | X | | X | |
| Dispense study drug [6] | | | X | | X | | | | | |
| Administration of study drug[7] | | | | ↔ | ↔ | ↔ | ↔ | ↔ | X | |
| 12-lead ECG | X | | | | | | | | X[4] | |
| Vital signs and weight[8] | X | | | | X | | X | | X | X |
| AE/SAE monitoring[9] | | | | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Prior/concomitant medications | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

[1] Following pre-screening, participants who continue to meet eligibility requirements will undergo initial screening at the clinical site at V1. Only participants who meet all non-PSG based enrollment criteria undergo PSG at V2. Only if the AHI(4%) of V2 PSG is 7-50, inclusive, is the participant eligible for the V3 PSG. Mean AHI(4%) of V2 and V3 must be 10-45 inclusive for enrollment.
[2] V2 and V3 PSGs averages serve as baseline for calculation of PSG efficacy outcomes.
[3] Final study eligibility is determined the morning after the V3 PSG, based on V2 and V3 PSG read by the site (PSGs are read separately later by the central reading center for endpoint calculation); eligible participants are randomized.
[4] Can be conducted either evening or morning of PSG.
[5] Additional pregnancy testing may be done at other times when clinically indicated, e.g. if a menstrual cycle is missed or when pregnancy is otherwise suspected.
[6] Run-in study drug distributed at V3 following randomization (can be distributed up to two days later if necessary for scheduling); full dose study drug distributed at V4; unused study drug is returned to the site at V4 (run-in drug) and V6 (full-dose drug).
[7] Study drug is dosed immediately prior to lights-out, including at V5 and V6 PSG; dose for PSG nights is from the supply provided to the participant at V4.
[8] On PSG visits vital signs are measured and recorded both evening of PSG and morning after PSG.
[9]Sites contact participants by phone mid-week of run-in period (day 3-4) and mid-week first week of full-dose period (day 10-11), for AE/SAE monitoring and review of study procedures; AE/SAE collection begins with randomization

| Procedures | Screening[1] and Baseline PSG[2] | | | Treatment Period | | | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | PSG V2 | PSG V3 | QHS Run-in dose | | QHS Full-dose | | | | V7 |
| | | | | At-home dosing | Clinic V4 | At-home dosing | PSG V5 | At-home dosing | PSG V6 | |
| **Trial Day/Duration** | **Up to 4 weeks** | | | **Day 1-7 ± 2** | **Day 7 ± 2** | **Day 8-21 ± 2** | **Day 21 ± 2** | **Day 22-28 ± 2** | **Day 28 ± 2** | **Day 42± 2** |
| ESS, Short SAQLI, PGI-S, Quantity and Quality of Work, PROMIS sleep impairment, PROMIS sleep disturbance, PROMIS fatigue | X[10] | | X | | | | | | X | |
| CSSA | X | | | | | | | | | X |
| DSST, PVT, VOLT[11] | | | X | | | | X | | X | |

Abbreviations: AE = adverse event; CSSA = cocaine selective severity assessment; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EoS = end of study; ESS = Epworth Sleepiness Scale; PGI-S = Participant Global Impression -Severity; PROMIS = Patient Reported Outcomes Measurement Information Systems; PSG = polysomnography; PVT = psychomotor vigilance task; QHS = each night; SAE = serious adverse event; SAQLI = Sleep Apnea Quality of Life Index; VOLT = Visual Object Learning Task; WOCBP = women of childbearing potential.

[10] At V1 only PGI-S is measured (for use as enrollment criterion). At V3 and V6 all listed endpoints are measured, including PGI-S, the evening of the PSG exam.
[11] Administer DSST, PVT and VOLT morning after PSG

# 2 Introduction

## 2.1 Study Rationale

Previous studies conducted by the sponsor and academic investigators indicate that the combination drug composed of atomoxetine with either aroxybutynin (designated AD109) or with trazodone (designated AD504)is effective for the treatment of OSA. The present study is designed to advance dose-finding for AD109 and AD504 over a 1-month period of dosing in participants with moderate to severe OSA.

## 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 of the more serious 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 has 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 variable 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 adverse health outcomes and increased mortality. Alternative options, such as drugs that activate the pharyngeal muscles, are needed.

### 2.2.3 Biological Rationale

AD109 and AD504 are new fixed dose drug combinations of atomoxetine and aroxybutynin (AD109) or trazodone (AD504) 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. Aroxybutynin 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. Trazodone is approved for the treatment of major depressive disorder (MDD) and, at lower doses, is commonly used off-label for insomnia. Trazodone is active at multiple receptors including serotonergic and adrenergic, and is a weak

serotonin reuptake inhibitor. MARIPOSA/APC-005 is designed to advance dose-finding for AD109 and AD504 over a 1-month period of dosing, longer duration than previous studies.

# 3 Endpoints

| | Endpoints |
|---|---|
| **Primary** | • Change in AHI4, combined Ato/Aroxy dose arms vs. combined placebo arms |
| **Secondary** | • Change in AHI4, combined Ato + Trazo dose arms vs combined placebo arms<br>• Change in AHI4, combined Ato dose arms vs. combined placebo arms |
| **Tertiary** | • Change in AHI4, HB4, ODI4, AHI3a; cross-arm comparisons<br>• Change in PGI-S, Short SAQLI, PROMIS sleep impairment, PROMIS sleep disturbance, PROMIS fatigue, ESS, QQ; cross-arm comparisons<br>• Total time with $SaO_2$ <90%, PSG nights<br>• Proportion of participants with ≥50% reduction in AHI4<br>• PSG sleep and arousal parameters<br>• PSG respiratory parameters |
| **Safety Endpoints** | • Physical exam, vital signs, clinical laboratory assessment<br>• Spontaneous adverse events, including the post-dosing period<br>• DSST, PVT, VOLT<br>• PSG parameters: heart rate, ECG parameters (including QT), EEG, oximetry |

Abbreviations: AHI3a = apnea-hypopnea index based on 3% hypopnea desaturation plus arousals; AHI4 = apnea-hypopnea index based on 4% hypopnea desaturation; Aroxy = aroxybutynin; Ato = atomoxetine; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EEG = electroencephalogram; ESS = Epworth sleepiness Scale; HB4 = hypoxic burden based on 4% hypopnea desaturation; ODI4 = oxygen desaturation index based on 4% desaturation definition; OSA = obstructive sleep apnea; PGI-S = participant global impression – severity; PROMIS = Patient Reported Outcomes Measurement Information System; PSG = polysomnography; PVT = psychomotor vigilance test; QQ = Quantity and Quality of Work VAS; $SaO_2$ = oxygen saturation; SAQLI = sleep apnea quality of life index; Trazo = trazodone; VOLT = Visual object learning task.

# 4 Study Design

## 4.1 Overall Design

The MARIPOSA Study (APC-005) is a randomized double-blind, placebo-controlled parallel arm study designed to advance dose-finding for AD109 and AD504 over a 1-month period of dosing.

Participants will undergo initial pre-screening to determine potential study eligibility. Participants 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). Participants who meet all non-PSG enrollment criteria at V1 are eligible

for the first screening/baseline PSG at Visit 2. If the AHI(4%)[hypopneas defined by 4% oxygen desaturation] of the V2 PSG is between 7-50, inclusive, ≤25% of events are central or mixed apneas and PLM arousal index ≤15, the participant is eligible for the second screening/baseline PSG at V3. The AHI enrollment criterion is met if the mean AHI(4%) of the V2 and V3 PSGs is 10-45, inclusive and ≤25% of events are central or mixed apneas and PLM arousal index ≤15 on PSG at V3. For enrollment purposes, the V2 and V3 PSGs are read by the site (endpoint calculation is based on a separate re-read of the PSGs at a later date by the central reading center).

Participants who meet all enrollment criteria will be randomized to one of 8 parallel treatment arms. The first week of dosing will be with a lower dose run-in, followed by the full dose taken in weeks 2-4. Note that study drug for arms 1-4 is provided as a single tablet taken nightly immediately before lights out, whereas study drug for arms 5-8 is divided into one tablet and one capsule, **both** to be taken nightly immediately before lights out:

1. **Atomoxetine 75 mg/aroxybutynin 5 mg tablet (n = 40)**
    - Week 1: atomoxetine 37.5 mg/aroxybutynin 2.5 mg tablet
    - Weeks 2-4: atomoxetine 75/aroxybutynin 5 mg tablet
2. **Atomoxetine 75 mg/aroxybutynin 2.5 mg tablet (n = 40)**
    - Week 1: atomoxetine 37.5/aroxybutynin 2.5 mg tablet
    - Weeks 2-4: atomoxetine 75 mg/aroxybutynin 2.5 mg tablet
3. **Atomoxetine 75 mg tablet (n = 30)**
    - Week 1: atomoxetine 37.5 mg/placebo tablet
    - Weeks 2-4: atomoxetine 75 mg/placebo tablet
4. **Placebo tablet (n = 30)**
    - Week 1: placebo tablet
    - Weeks 2-4: placebo tablet
5. **Atomoxetine 75 mg tablet + Placebo capsule (n = 30)**
    - Week 1: atomoxetine 37.5 mg tablet + placebo capsule
    - Weeks 2-4: atomoxetine 75 mg tablet + placebo capsule
6. **Placebo tablet + placebo capsule (n = 30)**
    - Week 1: placebo tablet + placebo capsule
    - Weeks 2-4: placebo tablet + placebo capsule
7. **Atomoxetine 75 mg tablet + trazodone 100 mg capsule (n = 40)**
    - Week 1: atomoxetine 37.5 mg tablet + trazodone 50 mg capsule
    - Weeks 2-4: atomoxetine 75 mg tablet + trazodone 100 mg capsule
8. **Atomoxetine 75 mg tablet + trazodone 50 mg capsule (n = 40)**
    - Week 1: atomoxetine 37.5 mg tablet + trazodone 50 mg capsule

- Weeks 2-4: atomoxetine 75 mg tablet + trazodone 50 mg capsule

Study drug for the initial week of randomized drug treatment will be distributed to randomized participants the morning after the PSG of Visit 3. Participants will dose study drug each night at home immediately prior to lights out for the 7 day lower-dose run-in period. At completion of the run-in period, participants will return for Study Visit 4. Any unused drug from the run-in period will be collected, and participants will be evaluated for drug safety and tolerability. Full-dose study drug for the remaining 3 weeks of the study will be dispensed at Visit 4. After two weeks of at-home dosing with full dose study drug, participants return with their study drug for an inpatient PSG at V5. At the completion of the 4 week at-home dosing period all participants will return for an inpatient PSG night during the final night of dosing of study drug at Visit 6. The V5 and V6 PSG are centrally read for endpoint calculation, and do not need to be read by the site. An End of Study Evaluation will be conducted at V7, 2 weeks following the end of study drug dosing.

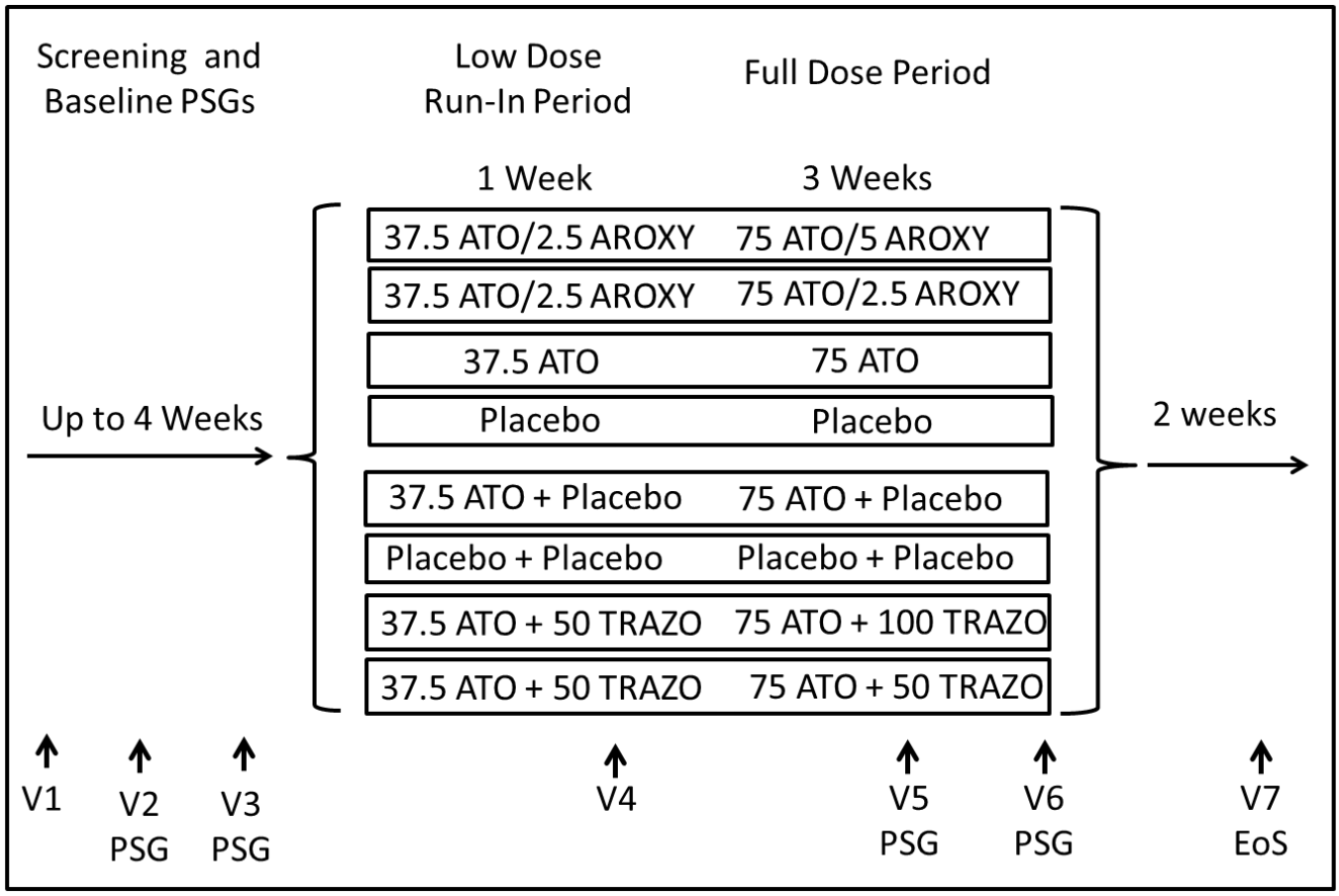
Adverse event and concomitant medication monitoring will occur at each study visit, and study sites contact participants by phone mid-week of the run-in period and mid-week of the first week of full-dose period, for adverse event and concomitant medication monitoring, and review of study procedures and visit schedule.

Overall study duration will be up to 10 weeks.

A total of 280 participants will be enrolled in the ratio indicated above (4 / 4 / 3 / 3 / 3 / 3 / 4 / 4)

Dose reduction is not permitted; dosing is discontinued if the study drug to which the participant is randomized is not tolerated. Participants who withdraw from the study will not be replaced.

**Figure 1: Overview of Study Design**




AROXY = aroxybutynin; ATO = atomoxetine; EoS = End of Study; PSG = polysomnography; TRAZO = trazodone; V = Visit

## 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 with either aroxybutynin (designed AD109) or trazodone (designated AD504) is effective for OSA, and that both drug components of the combinations are necessary for efficacy. The present study is designed to advance dose-finding for AD109 and AD504 over a 1-month period. AD109 at a dose of 75 mg atomoxetine/2.5 aroxybutynin was safe and effective in previous Phase 2 studies of up to 30 days duration. The present study will compare this dose to a higher dose containing 75 mg atomoxetine/5 mg aroxybutynin. The safety of 5 mg aroxybutynin is supported by previous studies of up to 8 days duration. Trazodone 100 mg combined with atomoxetine 75 mg was safe and effective in OSA in a single-dose crossover study conducted by Apnimed, and the present study will compare this to a lower dose containing 50 mg trazodone plus 75 mg atomoxetine.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AD109 and AD504 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 individuals 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 18 to 65 years of age for men and 18-75 for women, inclusive, at the Screening Visit.

**OSA Measures**

2. AHI: Mean AHI of V2 and V3 PSGs 10 to 45, inclusive, (Hypopneas defined by 4% oxygen desaturation).
3. PGI-S: >1, ie at least "very mild symptoms" at V1
4. ≤25% of events are central or mixed apneas at V2 baseline PSG

**Weight**

5. BMI between 18.5 and 38 kg/m$^2$ for men and 40 kg/m$^2$ for women, inclusive.

**Male participants:**

6. 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:**

7. 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.
8. 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 sterile (e.g. bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

**Informed Consent**

9. 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.

10. 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. Current clinically significant sleep disorder other than OSA.
2. Clinically significant craniofacial malformation or grade ≥3 tonsillar hypertrophy.
3. Clinically significant cardiac disease (e.g., rhythm disturbances, coronary artery disease or cardiac failure) or hypertension requiring more than 2 drugs for control (combination drugs count as 1 drug).
4. Long QT syndrome or family history of long QT syndrome
5. Clinically significant neurological disorder, including epilepsy/convulsions.
6. History of other major organ system disease including renal failure, lung disease, neuromuscular disease, or liver disease.
7. 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.
8. History of attempted suicide within 1 year prior to screening, or current suicidal ideation.
9. History of clinically significant urinary retention, gastric retention or other severe decreased gastrointestinal motility condition.
10. Severe or frequent gastroesophageal reflux or constipation
11. 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.
12. A significant illness or infection requiring medical treatment in the past 30 days as determined by investigator.
13. Clinically significant cognitive dysfunction as determined by investigator.

14. Untreated narrow angle glaucoma.
15. Women who are pregnant or nursing.

**Prior/Concomitant Therapy**

16. Participants with a history of using devices for OSA treatment, including CPAP, oral or nasal devices, or positional devices, may enroll as long as the devices have not been used for at least 2 weeks prior to first PSG and are not used during participation in the study (through V6).
17. History of chronic oxygen therapy.
18. Concomitant use of medications from the list of disallowed medications.
19. 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**

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

**Diagnostic Assessments**

21. Prolonged QT interval (> 450 ms in men or > 470 ms in women), hypokalemia, hypomagnesemia.
22. 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.
23. PLM arousal index >15

**Other Exclusions**

24. <5 hours typical sleep duration.
25. Night- or shift-work sleep schedule which causes the major sleep period to be during the day.
26. Employment as a commercial driver or operator of heavy or hazardous equipment.

27. Typically smoking more than 10 cigarettes or 2 cigars per day, or inability to abstain from smoking during overnight PSG visits.
28. Unwilling to use specified contraception.
29. History of regular alcohol consumption of more than 14 standard units per week (males) or more than 7 standard units per week (females), or unwillingness to limit alcohol consumption to no greater than 2 units/day (males), 1 unit per day (females). Alcohol is not to be consumed within 3 hours of bedtime or on PSG nights.
30. Unwilling to agree 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.
31. 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.
32. Participant considered by the investigator, for any reason, an unsuitable candidate to receive AD109 or AD504 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 (e.g. four 8 oz. cups of coffee), is permitted during the study period, consumed no less than 3 hours prior to bedtime.

3. Participants should abstain from smoking or chewing tobacco products during overnight PSG visits.

## 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 do not meet criteria for participation in the study. Rescreening, or repeating specific screening tests, is permitted with prior consent of the Sponsor if initial results were missing or uninterpretable or represented a transient or reversible status, or if confirming earlier eligibility is necessary because of concern of a change in the participant's status, or if protocol enrollment criteria are changed through protocol amendment. A minimal set of information on all participants who consent to participate 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, reason for screen failure, and any serious adverse events (SAEs).Study Treatment

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

## 5.7 Study Drug(s) Administered

Study drug is taken immediately prior to lights out, and consists of either 1 tablet (arms 1-4) or 1 tablet plus 1 capsule. (arms 5-8) The following formulations are used in this study (combined as described in Section 4.1):

| **Study Treatment Name:** | **Atomoxetine hydrochloride/ R-oxybutynin chloride** | **Atomoxetine hydrochloride** | **Trazodone hydrochloride** | **Matching Placebo** |
|---|---|---|---|---|
| **Dosage Formulation:** | Tablet | Tablet | Capsule | Tablet or capsule |

| | | | | |
|---|---|---|---|---|
| **Dosage Level:** | 37.5mg / 2.5mg<br>75mg / 2.5mg<br>75mg / 5mg | 37.5mg<br>75mg | 50mg<br>100mg | N/A |
| **Route of Administration:** | Oral | | | |
| **Dosing Instructions:** | 1 tablet administered with up to 240 mL water, OR<br>1 tablet and 1 capsule administered together with up to 240mL water | | | |
| **Storage/ Packaging/ Labeling:** | Store at room temperature in the labeled and provided HDPE bottles. | | | |

## 5.8 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 drugs received and any discrepancies are reported and resolved before use of the study drug.
2. Only participants enrolled in the study may receive study drugs and only authorized site staff may supply or administer study drugs. All study drugs 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 drug 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 drug to the Sponsor or designated third party or for preparing the study drug for destruction via incineration.

## 5.9 Measures to Minimize Bias

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

Returned study drug will not be re-dispensed.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study drug 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 drug assignment unless this could delay emergency treatment of the participant. If a participant's study drug 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 drug records at the site(s) to verify that randomization/dispensing has been done accurately.

## 5.10 Concomitant Therapy

Concomitant therapy with the medications listed below is **disallowed**. For medication that is typically used by the participant intermittently, occasionally, or as-needed (e.g. occasional use of a non-prescription sleep aid), it is sufficient that the medication not be used for at least one week prior to Visit 2 and for the duration of the study. Other disallowed medication would typically preclude enrollment unless the medication can be discontinued at least 1 month prior to Visit 2 without jeopardizing the participant's health or the stability of the participant's condition.

MAOIs or other drugs that affect monoamine concentrations (e.g., rasagiline) [MAOIs are contraindicated for use with atomoxetine or trazodone]

Norepinephrine Reuptake Inhibitors (NRIs)(e.g., duloxetine, reboxetine, venlafaxine, desvenlafaxine, milnacipran, levomilnacipran, maprotiline, viloxazine) and Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs)(e.g. bupropion, methylphenidate), nefazodone [Selective Serotonin Reuptake Inhibitors that do not strongly inhibit CYP 2D6 are allowed (e.g. citalopram, fluvoxamine, mirtazapine )

Trazodone and atomoxetine are disallowed except as study investigational product

Alpha-1 antagonists (e.g., tamsulosin, doxazosin)

Tricyclic antidepressants (e.g., desipramine)

Strong CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, duloxetine, quinidine, cinacalcet, bupropion)

Strong CYP3A4 inhibitors (e.g., ketoconazole)

Sedatives, sedative-hypnotics, and hypnotics (e.g. benzodiazepines, barbiturates, buspirone, nonbenzodiazepine "Z-drugs", orexin receptor antagonists)

Opioids

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

Wake-promoting agents (e.g. modafinil, armodafinil, solriamfetol)

Daily chronic use of $Beta_2$ agonists, (e.g., albuterol, salmeterol) (Intermittent or PRN use is acceptable)

Antipsychotics

Anticholinergics and anticholinesterase inhibitors

Sedating antihistamines

Pseudoephedrine, phenylephrine, oxymetazoline

Warfarin

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** 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

OTC topicals (e.g., topical pain relievers)

Osteoporosis drugs

## 5.11 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).

## 5.12 Stopping Criteria

### 5.12.1 Individual Participant Stopping Criteria

Incidents of abuse, diversion, or misuse of the study drug.

Incidents of clinically significant hallucinations (excluding sleep-related 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 drug.

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.

## 5.13 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, 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 drug
- Loss to follow-up
- Participant withdrew consent at own request
- Other

## 5.14 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.

# 6 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.

Safety and Efficacy Scales and Tests

- The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire with 8 questions. Participants 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 administered approximately the same time of day prior to PSG recordings on Visit 3 and Visit 6

- 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 Visit 1 as an enrollment criterion, at the baseline/screening PSG Visit 3 and at PSG Visit 6, at approximately the same time prior to each PSG recording.
- The Short SAQLI is a self-administered questionnaire with 15 questions as used in this study. The Short SAQLI is a sleep-specific quality of life questionnaire designed to capture the adverse impact of sleep apnea on 4 domains: daily functioning, social interactions, emotional functioning, and symptoms. Items are scored on a 7-point scale, and item scores are averaged to yield a composite total score. The Short SAQLI is administered at the baseline/screening PSG Visit 3 and at PSG Visit 6, at approximately the same time prior to each PSG recording.

- The Quantity and Quality of Work (QQ) scale was developed to measure the consequences of illness on work. Participants are asked to indicate on a VAS scale from 1 to 10 how much work they actually performed during regular hours compared with normal, and the quality of that work. The Quantity and Quality of Work scale is administered at the baseline/screening PSG Visit 3 and at PSG Visit 6, at approximately the same time prior to each PSG recording.

- PROMIS (Patient-Reported Outcomes Measurement Information System) sleep impairment, sleep disturbance, and fatigue measures were developed with modern psychometric techniques including item response theory to assess various self-reported aspects of sleep and daytime impairment. Items are based on 5 point scales, either frequency or intensity, with higher scores corresponded to greater sleep disturbance or sleep-related impairment. The PROMIS measures are administered at the baseline/screening PSG Visit 3 and at PSG Visit 6, at approximately the same time prior to each PSG recording.

- The Digit Symbol Substitution Test (DSST) measures a range of cognitive and motor operations including motor speed, attention, visuo-perceptual functions, and some aspects of associative learning. The DSST requires participants to match symbols to numbers according to a key located on the tablet computer screen. The DSST is used in this study primarily as a safety measure for psychomotor impairment related to residual next-day effects of study drug dosed at bedtime. The DSST is administered the morning after baseline/screening PSG Visit 3, PSG Visit 5, and PSG Visit 6, at approximately the same time after each PSG recording.

- The Psychomotor Vigilance Test (PVT) measures sustained attention and reaction time. Participants are instructed to press the screen of a tablet computer as quickly as possible after a visual cue appears. In addition to reaction time, the test records lapses, in which the screen is not pressed in response to a cue, and false-positives in which the screen is pressed prior to appearance of the cue. The PVT is administered the morning after baseline/screening PSG Visit 3, PSG Visit 5, and PSG Visit 6, at approximately the same time after each PSG recording.

- The Visual Object Learning Task (VOLT) measures memory and recall. Participants are shown 10 different shaded shapes, one at a time, and instructed to memorize them. During the recall phase of the test, participants are shown 20 object shapes some of which were previously shown, one at a time, and asked to accurately and quickly recall the shapes they have seen before. Four possible answers are available, ranging from "definitely yes" to "definitely no." The VOLT is administered the morning after baseline/screening PSG Visit 3, PSG Visit 5, and PSG Visit 6, at approximately the same time after each PSG recording.

- The Cocaine Selective Severity Assessment (CSSA) was originally designed to measure the signs and symptoms of cocaine withdrawal. The CSSA is used in this study as a safety measure to withdrawal symptoms that might be caused by AD109 or AD504, particularly the atomoxetine component, which affects the norepinephrine system, a system also affected by cocaine. The CSSA is interview-based and administered by study site personnel. Special training or equipment is not needed, and the assessment is administered according to brief written guidelines. The CSSA is administered at V1 and EoS V7.

### 6.1.1 Polysomnography

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 similar across the PSG study nights. The participants will be given 8 hours of time-in bed.
- Participants should be actively encouraged to spend at least 1/3 of the night in the supine position and at least 1/3 of the night in the lateral position on each night of study.

- Scoring: PSG studies of randomized participants will be scored by a centralized PSG center, blinded to treatment assignment. The V2 and V3 PSGs will also be scored separately by the study site solely for purposes of determining study eligibility. PSGs of individuals who are not randomized are not scored centrally.

## 6.2 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, aroxybutynin, and trazodone, and by Phase 1 and 2 safety data for the combination drugs AD109 and AD504. Safety assessments will include physical examinations, measurement of vital signs, monitoring and recording of AEs, SAEs, and pregnancies, and 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 the following:

- Cardiac effects: atomoxetine and trazodone are associated with adverse cardiac events, including arrhythmia and QT interval prolongation, and similar events have been reported in post-marketing experience for oxybutynin, which contains aroxybutynin.
- Urine outflow: atomoxetine and aroxybutynin are associated with urinary retention.
- Suicidal ideation: Both atomoxetine and trazodone carry boxed warnings for suicidal thoughts and behaviors, noting that in adults, the target population for the proposed OSA study, an increased risk was not identified.
- Daytime sleepiness: each of the three drugs can be associated with daytime somnolence.

### 6.2.1 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 or surgery.

### 6.2.2 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).

### 6.2.3 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.

### 6.2.4 Clinical Safety Laboratory Assessments

Refer to Section 8.2 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.

## 6.3 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 drug or the study, or that caused the participant to discontinue the study and/or study drug.

### 6.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from 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 drug 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.

### 6.3.2 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.

### 6.3.3 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.

### 6.3.4 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.

### 6.3.5 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.

## 6.4 Treatment of Overdose

For this study, any dose of atomoxetine greater than 75 mg, of aroxybutynin greater than 5 mg, or of trazodone greater than 100 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, aroxybutynin, and/or trazodone are no longer expected to be present systemically.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study drug 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.

## 6.5 Pharmacokinetics

PK parameters are not evaluated in this study.

# 7 Statistical Considerations

## 7.1 Sample Size Determination

Sample size was based on efficacy findings in previous Apnimed Studies. The present study will have >90% power to detect a treatment difference on the primary endpoint at a two-sided 0.05 significance level if the true difference between the active arm and placebo arm on AHI4 is 11 units and the within-subject standard deviation is 11.

## 7.2 Randomization

Randomization will be to treatment arms for which stock of medication is available at the study site.

## 7.3 Populations for Analyses

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

| Set | Description |
|---|---|
| Enrolled | All participants who signed the ICF (including screening failures). |
| Randomized | All participants who were randomized. |
| Modified Intent to Treat (mITT) Set | The mITT set comprises all participants who are randomized, take at least 1 dose of any of the study drugs, 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 Set | The Safety Set consists of all participants who are randomized and receive at least 1 dose of any of the study drugs. Participants will be analyzed for safety based on the drug received. |
| Per Protocol (PP) Set | The PP Population consists of all participants without any major protocol violations that could influence efficacy assessment. |

## 7.4 Interim Analyses

No interim analysis is planned.

# 8 Supporting Documentation and Operational Considerations

## 8.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 8.1.1 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.

### 8.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate 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.

### 8.1.3 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.

### 8.1.4 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.

### 8.1.5 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.

### 8.1.6 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.

### 8.1.7 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 drug development.

### 8.1.8 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.

A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinTrials.gov).

### 8.1.9 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.

### 8.1.10 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.

#### 8.1.10.1 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.

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; 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.

## 8.3 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.<br>• 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).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• 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.<br>• "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.<br>• 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.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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**<br><br>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**<br><br>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.<br><br>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**<br><br>The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br><br>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**<br><br>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.<br><br>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.<br><br>The Investigator will then record all relevant AE/SAE information in the eCRF.<br><br>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.<br><br>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.<br><br>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:<br><br>Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.<br><br>Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.<br><br>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.<br><br>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.<br><br>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.<br><br>The Investigator will use clinical judgment to determine the relationship.<br><br>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.<br><br>The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.<br><br>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.<br><br>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.**<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br><br>Contacts for SAE reporting can be found in the Study Reference Manual. |

All SAEs will be recorded from 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.<br><br>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).<br><br>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.<br><br>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.<br><br>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. |

## 8.4 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 drug.

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]<br>*Failure rate of <1% per year when used consistently and correctly.* |
|---|
| Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2]<br>Oral<br>Intravaginal<br>Transdermal |
| Progestogen-only hormonal contraception associated with inhibition of ovulation<br>Oral<br>Injectable |
| **Highly Effective Contraceptive Methods That Are User Independent**[1] |
| Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<br>IUD<br>Intrauterine hormone-releasing system (IUS)<br>Bilateral tubal occlusion |
| **Vasectomized partner**<br>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**<br>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 drug. 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.

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 drug 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.

## 8.5 Appendix 5: List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| AHI | Apnea-hypopnea index |
| Aroxy | aroxybutynin |
| Ato | atomoxetine |
| 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 |
| HRT | hormone replacement therapy |
| HB | Hypoxic burden |
| 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 |
| TRAZO | trazodone |
| ULN | upper limit of normal |
| US | United States |
| WOCBP | woman of childbearing potential |

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**Declaration of the Investigator**

**Title:** Phase 2 Randomized Double-Blind Placebo-Controlled Parallel-Arm Dose Finding Study to Compare Fixed Dose Combinations of Atomoxetine/Aroxybutynin (AD109) and Atomoxetine/Trazodone (AD504) to Atomoxetine alone or Placebo 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