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CLINICAL STUDY PROTOCOL

PHASE 3 RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED 1-YEAR PARALLEL-ARM STUDY TO COMPARE A FIXED DOSE COMBINATION OF AROXYBUTYNIN/ATOMOXETINE (AD109) TO PLACEBO IN OBSTRUCTIVE SLEEP APNEA (Protocol# APC-APN-304, LunAIRo Study)

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Version:	4.0
Protocol Date:	11 June 2025

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PROTOCOL SIGNATURE PAGE

Protocol Title	Phase 3 Randomized Double-Blind Placebo-Controlled 1-year Parallel-Arm Study to Compare a Fixed Dose Combination of Aroxybutynin/Atomoxetine (AD109) to Placebo in Obstructive Sleep Apnea (LunAIRo Study)
Protocol Identification	APC-APN-304
Study Phase	3
Sponsor	Apnimed

Sponsor Representatives

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

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6/11/2025

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Date

Protocol Revision History

Protocol Version	Protocol Date	Description
Original Protocol, Version 1.0	April 2, 2023	No sites were activated under Version 1.0.
Version 2.0	July 13, 2023	As detailed in the following Summary of Changes, Apnimed has introduced modifications to the protocol V1.0 (dated April 2, 2023). Content changes are specified in the table found in Section, 9.6, Appendix 5 with identification of the section in the new protocol. In addition to the specific changes detailed in the table, the protocol amendment number, version number, and date of this version have been updated throughout the title and signature pages, synopsis, and in the headers and footers.
Version 3.0	December 11, 2023	As detailed in the following Summary of Changes, Apnimed has introduced modifications to the protocol V2.0 (dated July 13, 2023). Content changes are specified in the table found in Section, 9.6, Appendix 5 with identification of the section in the new protocol. In addition to the specific changes detailed in the table, the protocol amendment number, version number, and date of this version have been updated throughout the title and signature pages, synopsis, and in the headers and footers.
Version 4.0	June 11, 2025	As detailed in the following Summary of Changes, Apnimed has introduced modifications to the protocol V3.0 (dated December 11, 2023). Content changes are specified in the table found in Section, 9.6, Appendix 6 with identification of the section in the new protocol. In addition to the changes detailed in the table, the sponsor address, protocol amendment number, version

		number, and date of this version have been updated throughout the title and signature pages, synopsis, and in the headers and footers.

Principal Investigator

By signing below, I, the Principal Investigator approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, electronic case report forms (eCRF) and any protocol-related documents (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Apnimed. I understand that the study may be terminated, or enrollment suspended at any time by Sponsor, or by me if it becomes necessary to protect the best interests of the study patients.

_____ _____

Signature Date

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Name (block letters)

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Phase 3 Randomized Double-Blind Placebo-Controlled 1 year Parallel-Arm Study to Compare a Fixed Dose Combination of Aroxybutynin/Atomoxetine (AD109) to Placebo in Obstructive Sleep Apnea (LunAIRo Study)
Protocol Name/Number: LunAIRo/APC-APN-304
Phase: 3
Sponsor: Apnimed, Inc.
Rationale: The combination drug composed of aroxybutynin and atomoxetine, designated AD109, is being developed by Apnimed for the treatment of obstructive sleep apnea (OSA). The present study, LunAIRo (APC-APN-304), is a Phase 3 study designed to examine the efficacy and safety of AD109 compared to placebo at 6-months and 1 year.
Overall Design:
The LunAIRo Study (APC-APN-304) is a randomized, double blind, placebo-controlled, parallel-arm 1-year parallel-arm study in participants with OSA who are intolerant to, or currently refuse, positive airway pressure (PAP) therapy. A screening visit and polysomnogram (PSG) will be conducted to establish that each participant meets study enrollment criteria. Enrolled participants will be randomized 1:1 to either AD109 or placebo. The first week of dosing will be with a lower dose (run-in) of AD109, or placebo, followed by the target dose taken 50-weeks, then a two-week period without dosing prior to the End of Study visit at 53 weeks.

1. **Aroxybutynin 2.5 mg/Atomoxetine 75 mg tablet (n = 320)**
    - Week 1: aroxybutynin 2.5 mg/atomoxetine 37.5 mg tablet
    - Weeks 2-51: aroxybutynin 2.5 mg/atomoxetine 75 mg tablet
2. **Placebo tablet (n = 320)**
    - Week 1: placebo tablet
    - Weeks 2-51: placebo tablet

The primary purpose of conducting this study is to show that AD109 is safe and superior to placebo for airway obstruction (AHI4). A key secondary purpose is to show that AD109 is superior to placebo for OSA symptoms (including PROMIS-Fatigue, PGI-C and PGI-S for Fatigue, PROMIS-Sleep Impairment).
Number of Participants:
A total of approximately 640 participants will be enrolled, randomized 1:1 to AD109 or placebo.
Study Duration:
The overall study duration for each participant will be up to 57 weeks, as follows:

- Screening, up to 4 weeks
- Randomized parallel-arm treatment
    - Run-in dose: 1 week
    - Target dose: 50 weeks
    - 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] & Baseline PSG[2]			APC-APN-304 Treatment Period														EOS
				QHS Low dose (run-in) Nights 1-7			QHS Target-dose Nights 8-360											
	V1	V2	V3				V4		V5			V6			V7			V8	V9
				C1	C2	C3		C4		C5	C6		C7	C8		C9	C10		
Study Day	**Day -28 to 1[3]**			**2[4]**	**5**	**15**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	**374**
Window (Days)				**0**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 4**
~Week	**Up to 4 wks**			**1**	**1**	**2**	**4**	**9**	**13**	**17**	**21**	**26**	**30**	**34**	**39**	**43**	**47**	**51**	**53**
Informed Consent	X																		
Demographics and medical history	X																		
Physical exam	X																		
Height	X																		
Vital signs, Day 1 of visit[5]	X	X	X				X		X			X			X			X	X

[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.
[2] V2 PSG serves as baseline for calculation of PSG efficacy outcomes.
[3] A longer screening period may be permitted with prior consent of the sponsor.
[4]Call 1 (C1) is the day after the first dose of IMP, as indicated by a window of "0" days, and can be considered completed by a phone call or other agreed mode of contact made to the participant even if the participant does not answer/respond; the next contact with the participant can occur in the C2 window.
[5] Vital signs are measured at clinic visits and on admission to PSG unit.

Procedures	Screening[1] & Baseline PSG[2]			APC-APN-304 Treatment Period															EOS
				QHS Low dose (run-in) Nights 1-7			QHS Target-dose Nights 8-360												
	V1	V2	V3				V4		V5			V6			V7			V8	V9
				C1	C2	C3		C4		C5	C6		C7	C8		C9	C10		
Study Day	**Day -28 to 1[3]**			**2[4]**	**5**	**15**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	**374**
Window (Days)				**0**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 4**
~Week	**Up to 4 wks**			**1**	**1**	**2**	**4**	**9**	**13**	**17**	**21**	**26**	**30**	**34**	**39**	**43**	**47**	**51**	**53**
Day 2 vitals[6]		X							X			X						X	
Weight	X						X		X			X			X			X	X
Clinical lab	X											X[7]						X[7]	
CYP2D6 sample[8]	X																		
Drugs of abuse[9]	X																		
Pregnancy test[10]	X																		
PSG		X							X			X						X	
24hr ABPM[11]			x | X				x | X												
Randomization			X																

[6] Only applies to PSG visits, which occur from evening of Day 1 to morning of Day 2; Morning vital signs measured about 1 hour after end of PSG
[7] Can be conducted either day of or day after PSG.
[8] Indicates blood sample collection, not testing; blood samples are sent to clinical laboratory for storage prior to CYP2D6 testing
[9] A confirmatory gas chromatography-mass spectrometry test is conducted for positive results from screening immunoassay drug test.
[10] 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.
[11] 24hr ABPM is not required for participation in the study. Participants who agree to ABPM come to the site the day before V3 and V4 (indicated in SoA by "x| X") to be fitted with the device and recording to be started. The device is removed ~24 hours later by the site.

Procedures	Screening[1] & Baseline PSG[2]			APC-APN-304 Treatment Period															EOS
				QHS Low dose (run-in) Nights 1-7			QHS Target-dose Nights 8-360												
	V1	V2	V3				V4		V5			V6			V7			V8	V9
				C1	C2	C3		C4		C5	C6		C7	C8		C9	C10		
Study Day	**Day -28 to 1[3]**			**2[4]**	**5**	**15**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	**374**
Window (Days)				**0**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 4**
~Week	**Up to 4 wks**			**1**	**1**	**2**	**4**	**9**	**13**	**17**	**21**	**26**	**30**	**34**	**39**	**43**	**47**	**51**	**53**
Dispense IMP			X[12]				X		X			X			X				
IMP accountability							X		X			X			X			X	
Dose IMP[13]			X	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	X	
12-lead ECG	X											X							X
AE/SAE monitoring[14]			↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Concomitant therapy	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
ESS		X					X		X			X			X			X	X
PROMIS SI		X					X		X			X			X			X	X
PROMIS F	X	X					X		X			X			X			X	X
PGI-S Fatigue		X					X		X			X			X			X	X
PGI-C Fatigue							X		X			X			X			X	X
DSST		X							X			X						X	
PVT		X							X			X						X	

[12] IMP provided at V3 consists of 1 blister with 7 days of low dose run-in and 1 bottle with 33 days of target dose or placebo.
[13] Study drug is dosed within 30 minutes of bedtime at home, and at lights-out of PSGs; dose for PSG nights is from the supply provided to the participant at prior visits, which should be brought by patient to site visits.
[14] AE/SAE collection begins with randomization; includes asking about sleepiness-related motor vehicle accident (MVA)

Procedures	Screening[1] & Baseline PSG[2]			APC-APN-304 Treatment Period															EOS
				QHS Low dose (run-in) Nights 1-7	QHS Target-dose Nights 8-360														
	V1	V2	V3				V4		V5			V6			V7			V8	V9
				C1	C2	C3		C4		C5	C6		C7	C8		C9	C10		
Study Day	Day -28 to 1[3]			2[4]	5	15	30	60	90	120	150	180	210	240	270	300	330	360	374
Window (Days)				0	± 2	± 2	± 4	± 4	± 4	± 6	± 6	± 6	± 6	± 6	± 6	± 6	± 6	± 6	± 4
~Week	Up to 4 wks			1	1	2	4	9	13	17	21	26	30	34	39	43	47	51	53
VLT		X							X			X						X	
MADRS-S	X	X					X		X			X			X			X	X
Spielberger	X	X					X		X			X			X			X	X
M-CSSA																			X

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; C = contact/call; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EoS = end of study; ESS = Epworth Sleepiness Scale; IMP = investigational medicinal product; M-CSSA = Modified cocaine selective severity assessment; PROMIS = Patient Reported Outcomes Measurement Information Systems, SI = Sleep Impairment, F = Fatigue; MADRS-S = self-reported Montgomery-Asberg depression rating scale; PGI-C = patient global impression change; PGI-S = patient global impression severity; PSG = polysomnography; PVT = psychomotor vigilance test; QHS = each night; SAE = serious adverse event; Spielberger = short version of Spielberger anxiety inventory; VLT = verbal learning task.

2 Introduction

2.1 Study Rationale

The combination drug composed of aroxybutynin and atomoxetine, designated AD109, is being developed by Apnimed for the treatment of obstructive sleep apnea (OSA). Phase 2 studies of increasing duration have been conducted for AD109. The MARIPOSA Study (APC-005) was a parallel-arm study that established the efficacy and safety of AD109 over a 1-month period of dosing. The present study, APC-APN-304, is a Phase 3 study designed to examine the efficacy and safety of AD109 vs placebo at 6-months and 1-year of dosing in participants who are intolerant to, or currently refuse, PAP.

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 twenty 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 and falls in oxygenation 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 most patients recommended treatment with positive airway pressure (PAP), 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 PAP 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 PAP 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 PAP 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 thepharyngeal muscles, are needed.

2.2.3 Biological Rationale

AD109 is a new fixed dose drug combination of aroxybutynin and atomoxetine being developed for OSA. 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. Atomoxetine is a pre-synaptic norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder in children and adults.
AD109 targets two neurochemical pathways at the hypoglossal nucleus which control the upper airway musculature during sleep: excitatory signaling (atomoxetine) and blockade of inhibitory signaling (aroxybutynin). Aroxybutynin also mitigates disruption of sleep caused by atomoxetine.

3 Endpoints

Objectives	Endpoints/Assessments
Primary Objectives Compare efficacy on airway obstruction of AD109 vs placebo in participants with mild to severe OSA at 26 weeks	**Primary Endpoint** • Change from baseline in apnea-hypopnea index based on 4% hypopnea desaturation (AHI4) at week 26
Secondary Objectives Compare efficacy on OSA symptoms and oxygenation of AD109 vs placebo in participants with mild to severe OSA at 26 weeks	**Key Secondary Endpoints** • Change from baseline in ODI3 at week 26 • Change from baseline in HB4 (on the natural log scale) at week 26 • Proportion of participants with ≥50% reduction in AHI4 at 26 weeks • Change from baseline in PROMIS-Fatigue T-score at week 26 **Secondary Endpoints** • Change from baseline in PGI-S for fatigue at week 26 • PGI-C for fatigue at week 26 • Change from baseline in ESS at week 26 • Change from baseline in PROMIS-Sleep Impairment T-score at week 26

Tertiary Objectives	Tertiary Endpoints
Compare efficacy on airway obstruction and OSA symptoms of AD109 vs placebo in participants with mild to severe OSA at 51 weeks	The following are assessed as change from baseline at week 51 or as specified • AHI4 • ODI3 • HB • Proportion of participants with ≥50% reduction in AHI4 at week 51 • PROMIS-Fatigue T-score • PGI-S for Fatigue • PGI-C for fatigue at week 51 • ESS • PROMIS-Sleep Impairment T-score
Exploratory Objectives	**Exploratory Endpoints**
Examine effects of AD109 on PSG sleep parameters, additional measures of airway obstruction, and at additional time points.	• Sleep architecture and sleep stage distribution at week 13, 26 and 51 • Above listed measures (Primary, Secondary, Tertiary) at week 13 • Percent of participants with AHI4<15, <10 and <5 at week 13, 26 and 51 • Proportion of participants with AHI4 reduction of ≥ 30% to ≥ 90% by 10% increments at week 13, 26 and 51 • Change from baseline in AHI3a, HB3a, and ODI4 at week 13, 26 and 51, as applicable • Change from baseline in Non-Rapid Eye Movement Apnea-Hypopnea Index [NREM AHI] at week 13, 26 and 51 • Change from baseline in Rapid Eye Movement Apnea-Hypopnea Index [REM AHI] at week 13, 26 and 51 (excluding participants whose PSG has <10 minutes of REM sleep) • Change from baseline in supine AHI4 [AHI4S] at week 13, 26 and 51 (excluding participants whose PSG has <10 minutes of supine sleep) • Change from baseline in Total sleep time (TST) and percentage of TST in sleep stages (sleep efficiency [SE]; wake after sleep onset [WASO]; sleep onset latency [SOL]; Stage N1% [N1P], Stage N2% [N2P], Stage N3% [N3P], Stage R% [RP])

	• Change from baseline in Arousal Indices (Arousal Index - Respiratory [ARIR]; Arousal Index - total [ARI]) • Change from baseline in OSA severity category (None, Mild, Moderate and Severe) at week 13, 26 and 51 • Proportion of patients with loud breaths (i.e., snoring)
Safety Objectives Evaluate the safety and tolerability of treatment with AD109 in patients with mild to severe OSA	**Safety Assessments** • Physical exam, vital signs (including 24hr ABPM), clinical laboratory assessment, ECG • Adverse events, including during the post-dosing period • DSST • PVT • Verbal learning task • M-CSSA • MADRS-S • Spielberger
Abbreviations: ABPM = ambulatory blood pressure monitoring; AHI3a = apnea-hypopnea index based on 3% hypopnea desaturation plus arousals; AHI4 = apnea-hypopnea index based on 4% hypopnea desaturation; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; ESS = Epworth sleepiness Scale; HB4 = hypoxic burden based on 4% hypopnea desaturation; MADRS-S = self-reported Montgomery-Asberg depression rating scale; M-CSSA = Modified cocaine selective severity assessment; ODI3 = oxygen desaturation index based on 3% hypopnea desaturation; OSA = Obstructive Sleep Apnea; PGI-C = patient global impression change; PGI-S = patient global impression severity; PROMIS = Patient Reported Outcomes Measurement Information System; PSG = polysomnography; PVT = psychomotor vigilance test; SE = Sleep Efficiency; SOL =Sleep Onset Latency; Spielberger = short version of Spielberger anxiety inventory; TST = Total Sleep Time; WASO = Wake After Sleep Onset	

4 Study Design

4.1 Overall Design

The LunAIRo Study (APC-APN-304) is a randomized, double blind, placebo-controlled, 1-year parallel-arm study of AD109 vs placebo in participants with mild to severe OSA who are intolerant of, or currently refuse, PAP. A screening visit and PSG will be conducted to establish, in combination with patient-reported outcomes assessments (PROs) and other criteria, that each participant meets study enrollment criteria.

A screening/baseline PSG is conducted at V2 and is read by the central PSG reading center. For enrollment the AHI4 (hypopneas defined by 4% oxygen desaturation) of the V2 PSG must be >5 and ≤45, with ≤ 25% central or mixed apneas (as proportion of total apneas + hypopneas), and PLM arousal index ≤15.

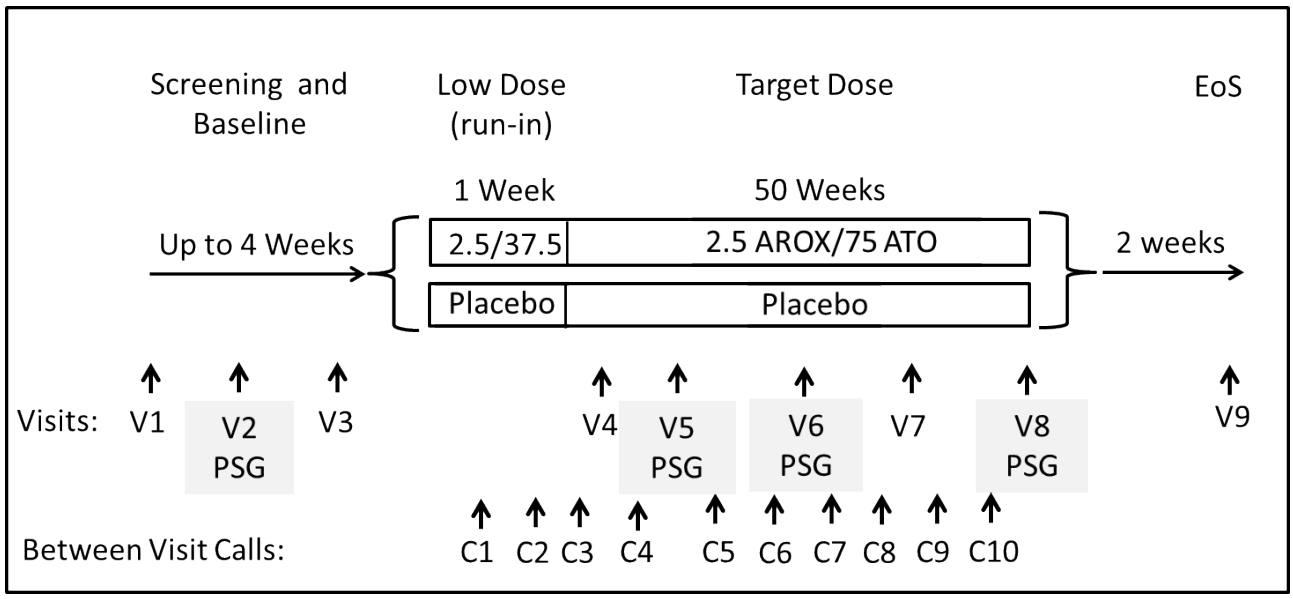
Participants who meet all eligibility criteria will be randomized to one of 2 parallel treatment arms. Enrollment will be stratified according to baseline AHI (<15, 15 to 30, >30) and PROMIS-Fatigue raw score (<25 vs ≥25); to ensure representative distribution of baseline AHI severity, the size of AHI strata will be controlled through enrollment limits, with AHI <15 representing

~20-40% of patients, AHI 15to 30 representing ~20-40% of patients, and AHI >30 representing ~20-40% of patients.
The first week of dosing will be with a lower dose of AD109 (run-in) or matched placebo, followed by the target dose taken for the duration of the study.

1. **Aroxybutynin 2.5 mg/Atomoxetine 75 mg tablet (n = 320)**
   - Week 1: aroxybutynin 2.5 mg/atomoxetine 37.5 mg tablet
   - Weeks 2-51: aroxybutynin 2.5 mg/atomoxetine 75 mg tablet
2. **Placebo tablet (n = 320)**
   - Week 1: matched placebo tablet
   - Weeks 2-51-: matched placebo tablet

Dose reduction is not permitted. Dosing is discontinued if the study drug to which the participant is randomized is not tolerated. Note that participants who discontinue dosing are encouraged to continue all other study activities for the full duration of the study.

Figure 1 Overview of Study Design



AROX = aroxybutynin; ATO = atomoxetine; C = contact/call; EoS = End of Study; PSG = polysomnogram; V = visit

4.2 Detailed Design

4.2.1 Pre-Screening

Participants who are identified as potentially eligible for enrollment by evaluation of the study site's database or through an initial online screening questionnaire or similar methods are contacted by telephone for additional pre-screening to confirm initial eligibility.

4.2.2 Visit 1

Individuals who remain eligible for the study following pre-screening attend Visit 1. Study eligibility for non-PSG based enrollment criteria are determined at Visit 1. Only individuals who are found to be eligible on all non-PSG criteria at Visit 1, including results of clinical laboratory testing that are not available until several days post-visit, continue further screening.
The following activities occur at Visit 1:

- Informed consent
    - Per Good Clinical Practice (GCP) guidelines when conducting a trial, the patient's primary care provider should be informed about the subject's enrollment in the trial, after obtaining the subject's consent to release this information.
- After consent, contact information is recorded for the patient's primary care provider and the investigator informs the provider about the participant's involvement in the study. Being under the care of a primary care provider is not required for participation in the study but should be encouraged.
    - Per GCP, during and following a subject's participation in the trial the investigator should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware (including medical conditions present at baseline that may require ongoing management such as hypertension or diabetes).
    - Enrolled participants are not prohibited from initiating PAP during the trial if deemed by the participant's primary care provider to be in the participant's best medical interest. IMP dosing can continue if PAP is initiated.
- Demographics and medical history, including medications and history of PAP use or other treatments for OSA, and confirmation of PAP failure or refusal.
- Physical examination, height, weight, vital signs, clinical laboratory testing, collection of samples for CYP2D6 testing, urine drugs of abuse test, pregnancy test, 12-lead ECG
- PROMIS-Fatigue
    - Raw score ≥17 required for enrollment
- MADRS-S and Spielberger
    - MADRS-S responses that indicate thinking or planning suicide are exclusionary at V1, and should be clinically addressed as indicated.

4.2.3 Visit 2

Visit 2 is the screening/baseline PSG. Only individuals who are found to be eligible on all enrollment criteria assessed at Visit 1, including results of laboratory testing, continue to Visit 2. The following activities occur at Visit 2:

- Medical and concomitant therapy (medication or device) monitoring
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) are measured both the evening of admission to the PSG lab (day 1 of visit) and the morning after the PSG (day 2 of visit).
- PSG; V2 PSG will serve as baseline for calculation of PSG efficacy outcomes.
- The following PROs are assessed the evening of the PSG
    - ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, MADRS-S, Spielberger
- DSST, PVT and Verbal Learning Task are assessed the morning after the PSG.

Visit 2 PSG data are sent to the central PSG reading center. The central reading center contacts the site typically within 1 week with PSG results and whether the participant remains eligible for the study, and the site schedules the participant for Visit 3 or notifies the participant of ineligibility for the study, accordingly. As detailed in the site manual, the screening PSG may be repeated under certain circumstances if deemed inadequate to determine participant eligibility, such as inadequate total sleep time.

4.2.4 Visit 3

Only individuals who are found to be eligible on all enrollment criteria continue to Visit 3. Baseline 24hr ABPM is not required for participation in the study but is encouraged if permitted by the participant's schedule. Participants performing 24hr ABPM come to the site ~24hr prior to Visit 3 to be fitted with the ABPM device (recorded as initial part of Visit 3). Participants resume normal daily activities for the remainder of the day and overnight, and return to the site the next day for device removal by site staff followed by the remainder of Visit 3 activities.
The following activities occur at Visit 3:

- 24hr ABPM (participating individuals).
- AE/SAE and concomitant therapy (medication or device) monitoring
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) are measured (including for participants who measured 24hr ABPM).
- Prior to randomization confirm PAP refusal in the context of V2 PSG results.
- Randomization of qualifying participants.
- Participants are instructed on IMP dosing and IMP is dispensed.
    - IMP is dispensed as one blister package of 7 tablets of the run-in dose, and 1 bottle of 33 tablets of target dose. All 7 tablets of the run-in dose are used prior to use of full-dose tablets from the bottled drug supply.
- Instruct participants on study procedures, including the following, and address scheduling of future study visits.

- IMP is taken nightly at home within 30 minutes of bedtime (and at lights out at PSG visits).
- Participants return with the bottle of study drug and empty blister pack at Visit 4 for drug accountability.

4.2.5 Contact/Call 1, 2 & 3

C1 is the day after the first dose of IMP, as indicated by a window of "0" days, and consequently can be considered completed by a phone call or other mode of contact by the site even if the participant does not answer/respond. Sites should encourage participants to contact/respond to the site if concerns or possible adverse events occur, including at times not indicated in the SoA, and sites may likewise initiate contact with participants more often than indicated in the SoA as clinically necessary.
The site contacts the participant at day 5 ± 2 (C2), during the low dose run-in of IMP, for AE/SAE and concomitant therapy (medication or device) monitoring. Participants who are deemed intolerant to the run-in dose discontinue IMP dosing but are encouraged to continue with all subsequent activities of the study as listed in the SoA, for the full duration of the study. An unscheduled site visit is arranged and conducted if clinically indicated for IMP tolerability issues.
The site contacts the participant on day 15 ± 2 (C3) for AE/SAE and concomitant therapy (medication or device) monitoring. Participants who are deemed intolerant to the full dose discontinue IMP but are encouraged to continue with all subsequent study activities. Dose decrease is not permitted. An unscheduled site visit is arranged and conducted if clinically indicated for IMP tolerability issues.
Sites should review study procedures and scheduling with participants during C1-C3 as needed.

4.2.6 Visit 4

V4 takes place at Day 30 ± 4.
Participants performing 24hr ABPM come to the site ~24hr prior to V4 to be fitted with the ABPM device (recorded as initial part of Visit 4). Participants resume normal daily activities for the remainder of the day and overnight, and return to the site the next day for the remainder of Visit 4 activities after the device is removed by site staff.
Participants must return to V4 with remaining IMP. Drug accountability is conducted, and **the remaining IMP is returned to the participant to be used until empty**, prior to starting the additional IMP supply that is dispensed at V4.
The following activities occur at Visit 4:

- 24hr ABPM (participating individuals).
- AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature; including for participants who measured 24hr ABPM) and weight
- ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, PGI-C, MADRS-S, Spielberger

- Review of study procedures and future study visits
- Drug accountability
- Dispense additional 2-month supply of study drug (33 count bottles, 2 bottles dispensed)

4.2.7 Contact/Call 4

The site contacts the participant on day 60 ± 4 (C4) for AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring and review of study procedures and future study visits.

4.2.8 Visit 5

V5 takes place at Day 90 ± 4 and includes overnight PSG.
Participants return to V5 with remaining IMP and any empty IMP bottles. Drug accountability is conducted.
If the participant arrives at the site without previously dispensed IMP, the IMP should be retrieved whenever practicable.
Prior to proceeding with additional visit activities, the site confirms with the participant that a dose of IMP has *not* been taken since the prior night, and instructs the participant that dose administration will be observed by site personnel. One dose of IMP is taken by the participant under observation by site personnel, at lights out at the start of the PSG. The time interval between dosing and lights out must be recorded, and typically should not exceed 15 minutes.
The following activities occur at V5:

- AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring.
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) are measured both the evening of admission to the PSG lab (day 1 of visit) and the morning after the PSG (day 2 of visit); weight
- PSG, with IMP dosing. If a participant initiated PAP during the study, the PSG is conducted without the use of PAP, and with IMP dosing (if dosing not otherwise discontinued).
- The following PROs are assessed the evening of the PSG
    - ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, PGI-C, MADRS-S, Spielberger
- DSST, PVT and Verbal Learning Task are assessed the morning after the PSG.
- Drug accountability
- Dispense additional 3-month supply of study drug (33 count bottles, 3 bottles dispensed)
- Review of study procedures and future study visits

V5 PSG data is sent to the central PSG reading center; findings of V5 PSG do not affect subsequent study activities. As detailed in the site manual, post-randomization PSGs typically are *not* repeated unless affected by technical factors clearly independent of possible effects of IMP on sleep parameters.

4.2.9 Contact/Call 5 & 6

The site contacts the participant on day 120 ± 6 (C5) and 150 ± 6 (C6) for AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring, and review of study procedures and future study visits.

4.2.10 Visit 6

V6 takes place at Day 180 ± 6, and includes overnight PSG.
Participants must return to V6 with remaining IMP. Drug accountability is conducted.
If the participant arrives at the site without previously dispensed IMP, the IMP should be retrieved whenever practicable.
Prior to proceeding with additional visit activities, the site confirms with the participant that a dose of IMP has *not* been taken since the prior night, and instructs the participant that dose administration will be observed by site personnel. One dose of IMP is taken by the participant under observation by site personnel at lights out at the start of the PSG. The time interval between dosing and lights out must be recorded, and typically should not exceed 15 minutes.
The following activities occur at V6:

- Blood collection for clinical laboratory testing, and ECG, can occur either the evening of or morning after the overnight PSG visit.
- AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring.
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) are measured both the evening of admission to the PSG lab (day 1 of visit) and the morning after the PSG (day 2 of visit); weight
- PSG, with IMP dosing. If a participant initiated PAP during the study, the PSG is conducted without the use of PAP, and with IMP dosing (if dosing not otherwise discontinued).
- The following PROs are assessed the evening of the PSG
    - ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, PGI-C, MADRS-S, Spielberger
- DSST, PVT and Verbal Learning Task are assessed the morning after the PSG.
- Drug accountability
- Dispense additional 3-month supply of study drug (33 count bottles, 3 bottles dispensed)
- Review of study procedures and future study visits

V6 PSG data is sent to the central PSG reading center; findings of V6 PSG do not affect subsequent study activities.

4.2.11 Contact/Call 7 & 8

The site contacts the participant on day 210 ± 6 (C7) and 240 ± 6 (C8) for AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring and review of study procedures and future study visits.

4.2.12 Visit 7

V7 takes place at Day 270 ± 6.
The following activities occur at Visit 7:

- AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring.
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) and weight
- ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, PGI-C, MADRS-S, Spielberger
- Review of study procedures and future study visits
- Drug accountability
- Dispense additional 3-month supply of study drug (33 count bottles, 3 bottles dispensed)

4.2.13 Contact/Call 9 & 10

The site contacts the participant on day 300 ± 6 (C9) and 330 ± 6 (C10) for AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring and review of study procedures and future study visits.

4.2.14 Visit 8

V8 takes place at Day 360 ± 6, and includes overnight PSG.
Participants must return to V8 with remaining IMP. Drug accountability is conducted**.**
If the participant arrives at the site without previously dispensed IMP, the IMP should be retrieved whenever practicable. If previously dispensed IMP is determined to be not available for dosing, the site can access replacement IMP for dosing.
Prior to proceeding with additional visit activities, the site confirms with the participant that a dose of IMP has *not* been taken since the prior night, and instructs the participant that dose administration will be observed by site personnel. One dose of IMP is taken by the participant under observation by site personnel at lights out at the start of the PSG. The time interval between dosing and lights out must be recorded, and typically should not exceed 15 minutes.
The following activities occur at V8:

- Blood collection for clinical laboratory testing; can occur either evening of or morning after the overnight PSG visit.
- AE/SAE (including sleepiness-related MVA) and concomitant therapy (medication or device) monitoring.
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) are measured both the evening of admission to the PSG lab (day 1 of visit) and the morning after the PSG (day 2 of visit); weight
- PSG, with IMP dosing. If a participant initiated PAP during the study, the PSG is conducted without the use of PAP, and with IMP dosing (if dosing not otherwise discontinued).
- The following PROs are assessed the evening of the PSG

    - ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, PGI-C, MADRS-S, Spielberger

- DSST, PVT and Verbal Learning Task are assessed the morning after the PSG.
- Drug accountability
- Review of study procedures and future study visits
- V8 PSG data are sent to the central PSG reading center.

4.2.15 End of Study Visit 9

Visit 9 is the End of Study visit and occurs approximately 2 weeks following cessation of study drug by participants, at Day 374 ± 4.
The following activities occur at Visit 9:

- AE/SAE (including possible effects of drug discontinuation and sleepiness-related MVA) and concomitant therapy (medication or device) monitoring.
- Vital signs (triplicate blood pressure, heart rate, respiratory rate, body temperature) and weight
- ECG
- ESS, PROMIS-Fatigue, PROMIS-Sleep Impairment, PGI-S, PGI-C, MADRS-S, Spielberger, M-CSSA

4.3 Scientific Rationale for Study Design and Dose

Previous Phase 2 studies of up to 30 days duration conducted by Apnimed support that the combination of aroxybutynin with atomoxetine, designated AD109, is effective for OSA, and that both drug components of the combination are necessary for efficacy. The present study is a longer-duration 1-year Phase 3 designed to demonstrate the long-term safety and efficacy of AD109 vs placebo.
A detailed description of the chemistry, pharmacology, efficacy, and safety of AD109 is provided in the Investigator's Brochure.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study 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 and outreach 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. ≥18 years of age at the time of informed consent.

OSA History and Measures

2. PSG criteria (collected at Visit 2)
    a. AHI4 (Hypopneas defined by 4% oxygen desaturation) of >5 and ≤45
    b. ≤ 25% central or mixed apneas (as proportion of total apneas + hypopneas)
    c. PLM arousal index ≤15
3. PROMIS-Fatigue: raw score ≥17 at Visit 1
4. PAP failure or PAP refusal
    a. PAP failure is defined as no PAP use for ≥3 months prior to randomization, or return/removal of PAP device from the home.
    b. PAP refusal is defined as refusal of PAP after prior positive sleep study, or prior refusal of provider-recommended sleep study due to unwillingness to consider PAP.

Weight

5. BMI between 18.5 and 40 kg/m^2 for men, or 42 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.
    a. Females of non-childbearing potential include 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

8. 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.
9. 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. Narcolepsy, restless leg syndrome requiring medication, REM sleep behavior disorder
2. Current bothersome symptoms of insomnia (difficulty initiating or maintaining sleep, as distinct from unrefreshing sleep or other symptoms attributable to OSA). Participants being treated for insomnia can be enrolled only if the condition is stable and generally controlled.
3. Pierre Robin, Treacher Collins, or other craniofacial malformation syndrome, or grade ≥3 tonsillar hypertrophy.
4. Clinically significant or medically uncontrolled cardiovascular disease, e.g., ventricular arrhythmia requiring medical or device therapy, unstable atrial fibrillation (including cardioversion, ablation, or change in antiarrhythmic regimen within past 3 months [patients in whom anticoagulation is indicated must be on such treatment for enrollment], or resting heart rate >100), untreated or unstable coronary artery disease (including revascularization within 3 months), cardiac failure, cerebrovascular event or transient ischemic attack or revascularization within 3 months.
5. Neuromuscular disorder (e.g., motor neuron disease, muscular dystrophy or myopathy, myasthenic syndrome); epilepsy; Parkinson, Alzheimer, or other neurodegenerative disease.
6. Schizophrenia, schizoaffective disorder, generalized anxiety disorder or bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) or International Classification of Disease tenth edition criteria.
7. Attempted suicide within 1 year prior to screening, or current suicidal ideation.
8. Severe or frequent constipation considered currently bothersome by the patient, or symptomatic gastric motility disorder.

9. Current bothersome symptoms of bladder outlet obstruction including difficulty initiating or maintaining urinary flow, straining, or sensation of incomplete bladder emptying; participants being treated with alpha-1 adrenergic antagonist for benign prostatic hypertrophy can be enrolled only if the condition is stable and generally controlled.
10. Active substance use disorder as defined in DSM-5, or other substance use 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. Positive screen for drugs with abuse liability is an important but not sole determinant of substance use disorder and study eligibility. Participants who use marijuana daily should be excluded.
11. A serious illness or infection in the past 30 days as determined by investigator.
12. Clinically significant cognitive dysfunction as determined by investigator.
13. Narrow angle glaucoma.
14. Women who are pregnant or nursing.

Prior/Concomitant Therapy

15. PAP can be initiated during the study if considered by the primary care provider and participant to be in the participant's best interest.
16. Participants with prior use of mandibular advancement devices, nasal devices, or sleeping position devices for the treatment of OSA may enroll as long as the devices are not used during participation in the study.
17. Participants with history of chronic oxygen therapy are excluded.
18. Participants with implanted devices for the treatment of OSA are excluded (e.g., hypoglossal nerve stimulator, or investigational devices).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

20. MADRS-S suicidal ideation response of thinking of or planning suicide (score ≥ 2).
21. Systolic blood pressure up to 140 mm Hg or diastolic blood pressure up to 90 mm Hg is allowed in participants not currently treated with antihypertensives. If the participant is

under the care of a healthcare provider managing blood pressure and on stable (at least 1 month) antihypertensive therapy, systolic blood pressure up to 145/90 is allowed at enrollment. If initial blood pressure (measured in triplicate, use average of final two readings) is above this enrollment threshold, it may be repeated up to a total of 3 times (each in triplicate) to confirm that the reading was not due to measurement technique or transient factors, with selection of the lowest repeated measure. The determination that blood pressure meets enrollment criteria involves the clinical judgment of the investigator interpreting blood pressure readings.

22. Unexplained or new identification of hepatic transaminases (AST or ALT) >2X the upper limit of normal (ULN) generally is exclusionary. However, elevation between 2-2.5 may be allowed with prior consent of the sponsor if evidence suggests it is due to nonalcoholic fatty liver disease (NAFLD) or other condition that would not be expected to acutely worsen or require medical intervention during the course of the study.
23. Total bilirubin >1.5X ULN (unless confirmed Gilbert syndrome).
24. Estimated glomerular filtration rate < 50 ml/min.
25. ECG abnormality indicative of clinically significant cardiac disease that may be adversely affected by AD109 (determined in consultation with the central ECG reading center and sponsor).

Other Exclusions

26. Night- or shift-work sleep schedule which causes the major sleep period to be during the day, including on a rotating basis.
27. Frequent travel or jet lag likely to interfere with study procedures or evaluations.
28. Employment as a commercial driver or other vehicle operator (includes independent contractors).
29. History of sleepiness-related MVA.
30. Unwilling to use specified contraception.
31. Any condition that in the investigator's opinion would present an unreasonable risk to the participant, including nature or severity of OSA symptoms, 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 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 and during the study.
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. Moderate consumption of caffeinated beverages, containing up to a total of 400 mg caffeine per day (e.g., two medium coffees), is permitted during the study period, consumed no less than 3 hours prior to bedtime.
2. Participants should refrain from more than 2 standard units per day for men or 1 unit/day for women of alcohol. Alcohol should not be consumed the evening of PSG.
3. Smoking more than 10 cigarettes or 2 cigars per day (or equivalent Vaping), or inability to abstain from smoking during overnight PSG visits is exclusionary.

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.

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants that meets the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography and reason for screen failure.
Rescreening, or repeating specific screening tests or steps at a time not otherwise specified in the protocol, is permitted with prior consent of the sponsor if initial results were missing or uninterpretable or represented a transient or reversible status that has resolved or stabilized, including with acute or ongoing treatment (e.g., poorly controlled hypertension or diabetes that has been adequately addressed to meet enrollment criteria), 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. Repeat testing for drugs of abuse is permitted based on the judgment of the investigator. The duration of the screening period can be extended

with prior agreement of sponsor if necessary to protect patient safety or ensure appropriateness of participation in the study.

6 Study Investigational Product

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

6.1 Study Drug(s) Administered

Study drug is taken at home within 30 minutes of lights out, and taken on PSG nights at the approximate time of lights out, and consists of 1 tablet. The following formulations are used in this study (as described in Section 4.1):

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

Dosing in the fully fasted state is not recommended; participants should avoid going to bed feeling hungry. A meal or snack no more than 3 hours prior to dosing is recommended.

IMP is initially dispensed as 1 blister strip of 7 doses of the run-in dose of AD109 (aroxybutynin 2.5 mg and atomoxetine 37.5 mg) or placebo, and 1 bottle of 33 doses of the target dose of AD109 (aroxybutynin 2.5 mg and atomoxetine 75 mg) or placebo. Subsequent supply is provided in 33 count bottles.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study 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.

6.3 Measures to Minimize Bias

Participants will be centrally randomized using interactive response technology (IRT). 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.
Unblinding of a participant's study treatment assignment is allowed if determined by the Investigator to be necessary to protect participant safety. Participant safety must always be the first consideration in making such a determination. Knowledge of the participant's treatment assignment should be limited to individuals who need to know to protect patient safety. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.
Unblinding related to functions of the Data Monitoring Committee (DMC) is described separately in the DMC charter.

6.4 Concomitant Therapy

Concomitant therapy with the medications listed below generally is disallowed. However, if the medication is used at a sufficiently low dose, it may be permitted with prior approval of the sponsor.
A period of 1 month typically should pass between discontinuing a prohibited medication and screening, to allow determination that the patient's medical condition was stable, but this period can be shorter if appropriate in the clinical judgement of the investigator and with prior approval of the sponsor.
On a case-by-case basis with approval of the sponsor a medication that is typically disallowed can be used to treat an intercurrent illness or condition that arises during the course of the study; consideration will be given to whether IMP dosing and/or other study activities will be temporarily paused in such circumstance. The sponsor must approve any such plans for temporary interruption.

- MAOIs or other drugs that affect monoamine concentrations (e.g., rasagiline, isocarboxazid, phenelzine, selegiline, tranylcypromine, linezolid, methylene blue, procarbazine) [MAOIs are contraindicated for use with atomoxetine)
- Norepinephrine Reuptake Inhibitors (e.g., atomoxetine, reboxetine, viloxazine)

- Tricyclic antidepressants (e.g., amitriptyline, clomipramine, amoxapine, desipramine, doxepin, imipramine, nortiptyline, protriptyline, trimipramine)
- Strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine)
- Strong CYP3A4 inhibitors (e.g., oral ketoconazole, ceritinib, clarithromycin, idelalisib, indinavir, oral itraconazole, mibefradil, nefazodone, nelfinavir, ribociclib, ritonavir, saquinavir, telithromycin, tucatinib, voriconazole)
- St John's Wort
- Barbiturates (e.g., phenobarbital, amobarbital, butalbital, methohexital, primidone, secobarbital)
- Buspirone
- Opioids (e.g., hydrocodone, oxycodone, oxymorphone, morphine, codeine, fentanyl, hydromorphone, methadone, meperidine, tramadol, carfentanil, buprenorphine)
    - Includes combination drugs (e.g., oxycodone + acetaminophen, hydrocodone + acetaminophen, tramadol + acetaminophen)
- Muscle relaxants in participants >65 years of age (e.g., baclofen, carisoprodol, chlorzoxazone, cyclobenzabrine, dantrolene, metaxolone, methocarbamol, orphenadrine, tizanidine)
- Pressor agents (e.g., midodrine, droxidopa)
- Central agonist antihypertensives (alpha methyldopa, clonidine, guanabenz, guanfacine)
- Amphetamines (including dextroamphetamine, methylphenidate, dexmethylphenidate, methamphetamine, lisdexamfetamine) and other sympathomimetic amines (e.g., phentermine)
- Drugs when used primarily or exclusively for weight loss (e.g., bupropion-naltrexone, liraglutide [Saxenda®], semaglutide [Wegovy®], orlistat, phentermine-topiramate)
- Dopaminergic or antihistaminergic antiemetics (e.g., dimenhydrinate, meclizine, prochlorperazine, domperidone, olanzapine, metoclopramide, promethazine)
- Modafinil, armodafinil, solriamfetol, pitolisant
- Esketamine
- Antipsychotics (e.g., risperidone, quetiapine, olanzapine, ziprasidone, palperidone, aripiprazole, clozapine, asenapine, chlorpromazine, haloperidol)
- Oral anticholinergics (e.g., benztropine, tolterodine, darifenacin, trospium, solifenacin, oxybutynin)
- Cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine, tacrine)
- More than occasional use or brief course of first-generation sedating antihistamines (e.g., diphenhydramine, chlorphenamine, doxylamine, brompheniramine, hydroxyzine)
    - Includes combination drugs (e.g., ibuprofen + diphenhydramine, acetaminophen + diphenhydramine, naproxen + diphenhdramine)

Allowed medications include but are not limited to those listed below. Medications that do not have substantial effects on the central nervous system (CNS), respiration, or muscle activity are typically allowed even if not listed below.

- Benzodiazepines (e.g., alprazolam, chlordiazepoxide, clorazepate, diazepam, lorazepam, oxazepam, prazepam, quazepam, clonazepam, estazolam, temazepam, triazolam)
- Nonbenzodiazepine "Z-drugs" (zolpidem, zaleplon, eszopiclone) and orexin antagonists (e.g., suvorexant, daridorexant, lemborexant).
- Trazodone
- Most commonly used antihypertensives (angiotensin-converting-enzyme/angiotensin II receptor blocker inhibitors, calcium channel blockers, spironolactone, hydrochlorothiazide, etc.) [note that central agonist antihypertensives are prohibited, as listed under prohibited medications]
- Statins
- Gabapentin, pregabalin
- Selective Serotonin Reuptake Inhibitors that do not strongly inhibit CYP 2D6 or 3A4 are allowed (e.g., citalopram, escitalopram, duloxetine, fluvoxamine, mirtazapine, sertraline, venlafaxine)
- Proton pump inhibitors and histamine H_2 receptor blockers
- Antacids, proton pump inhibitors
- Non-sedating antihistamines (e.g., cetirizine, desloratadine, loratadine, fexofenadine, levocetirizine)
- Melatonin
- Non-steroidal anti-inflammatory drugs and acetaminophen
- Anti-asthmatics
- Antibiotics, topical antifungals
- Laxatives
- Immunomodulators
- Erectile dysfunction drugs
- Inhaled corticosteroids (e.g., fluticasone)
- Antidiabetics, including those that are associated with weight loss, such as GLP-1 agonists and SGLT-2 inhibitors, when used principally for the control of diabetes
- Ocular hypotensives and other ophthalmics (e.g., timolol)
- Hormonal therapy (e.g., estrogen replacement or anti-estrogens) and hormonal contraceptives
- Thyroid medications
- Anticoagulants
- Gout medications
- OTC topicals (e.g., topical pain relievers)
- Osteoporosis drugs

6.5 Discontinuation of Study Treatment

If a clinically significant finding is identified, the Investigator or qualified designee will determine if IMP dosing can continue and whether any change in participant management is

needed. IMP dosing, and/or other associated study activities, can be temporarily stopped and restarted to assess relationship of clinical findings to IMP, with prior agreement of Sponsor. IMP dosing can continue if PAP is initiated and no IMP stopping criteria have been met.

6.6 IMP Stopping Criteria

6.6.1 Individual Participant IMP Stopping Criteria

- Blood pressure or pulse increase that, in the judgement of the investigator, may be related to IMP and presents a safety risk to the individual participant considering baseline factors and comorbidities. The following values should be factored into a decision to discontinue IMP:
    - Pulse increase of greater than 15 bpm that results in an overall bpm to over 90; or pulse greater than 100 bpm
    - Blood pressure >160 systolic and/or >100 diastolic.

  Note that new or increased antihypertensive therapy is not itself a criterion for stopping IMP. Compliance with antihypertensive therapy can be encouraged and factored into clinical decisions about IMP continuation.
- Abuse, diversion, or misuse of IMP.
- Clinically significant hallucinations (excluding sleep-related hallucinations), amnesia, delusional thinking, delirium, manic symptoms, aggressive behavior, suicidality, homicidally, agitation, confusion, or convulsions/seizures.
- SAE considered related to study drug.
- Acute urinary obstruction.
- Sleepiness-related MVA
- Any other AE or change in participant status that in the judgment of the Investigator necessitates the participant stopping IMP to protect participant safety or the safety of others.

Participants who discontinue from dosing IMP will be encouraged to continue all other study procedures through the end of the study.

Unless the subject specifically withdraws consent for such further follow up, all participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.

6.7 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. An investigator may ask a subject whether the subject wishes to provide continued follow-up and further data collection separately from interventional aspects of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information. Participants who withdraw from the study are requested to return for Visit 9/EOS activities approximately 2 weeks following cessation of IMP dosing.

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.

If a participant withdraws before completing the study the reason should be recorded to categories including the following:

- Loss to follow-up
- Participant withdrew consent at own request
- Other

6.8 Loss of Participants to Follow-Up

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

The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the participant on the importance of maintaining the assigned visit schedule.

In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record/eCRF.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each participant over the duration of the study, excluding any extra assessments that may be required for safety or technical issues, will not exceed approximately 50 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, as per the Investigator or designee's discretion.

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.

- PROMIS (Patient-Reported Outcomes Measurement Information System) sleep impairment 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 more severe or worse symptoms.

- MADRS-S (Montgomery-Asberg depression rating scale) is a nine-item diagnostic questionnaire typically used to measure the severity of depressive symptoms. Each item is based on a 3-point scale, with the overall score ranging from 0-27. Higher scores can indicate more severe depression or, in the context of this study, symptoms of OSA or effects of study drug.

- Patient Global Impression of Change (PGI-C)/Patient Global Impression of Severity (PGI-S) for Fatigue are each single-item scales of the patient's global, i.e., overall impression of either change from pre-treatment in fatigue (PGI-C) or severity of fatigue proximate to the timepoint measured (PGI-S).

- Spielberger Anxiety Inventory (STAI) - short form, is a self-completed questionnaire that aims to assess state anxiety (a temporary state influenced by the current situation where the respondent notes how he/she feels right now at this moment).

- 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 Verbal Learning Task (VLT) measures the ability to store words in working memory and long-term memory. In the learning phase, participants are instructed to pay attention to a list of one and two syllable words that are presented sequentially on a display, and to verbally repeat as many words as they can remember from the list. This cycle of presenting and repeating the same words is repeated three times. The recall phase is done after a prescribed delay. Participants are asked to verbally recall as many of the words as they can remember from the original list of words presented during the learning phase.

- 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 for withdrawal symptoms that might be caused by AD109, 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 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.

7.1 Polysomnography

- 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 participant's approximate 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 will be scored by a centralized PSG center, blinded to treatment assignment.

7.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Safety monitoring will be guided by the established safety profiles of aroxybutynin and atomoxetine, and by Phase 1 and 2 safety data for the combination drug AD109. 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. Layperson terms reported by the participant should be preferentially recorded.
    - Urine outflow
        - Slow initiation of urine flow, stopping/starting or weak flow, frequency or nocturia, or sensation of bladder not completely emptying. The term “urinary retention” should be reserved for incomplete bladder emptying (not slow or weak emptying).
    - Cardiovascular
        - Syncope, dizziness, palpitations, chest discomfort (cardiac vs. non-cardiac), symptom constellations of myocardial ischemia, possible cause of loss of normal consciousness.
    - Suicidal ideation
        - Thoughts about wish to be dead, non-specific thoughts of suicide, thoughts of method, specific plan, preparatory actions, intensity of ideation, suicide attempt, actual self-harm.
    - Daytime sleepiness
        - Record specific difficulties with daytime function, frequency, duration, time of day sleepiness occurs.
    - Motor vehicle accidents
        - Include whether participant felt sleepy proximate to the MVA, and other details that may inform cause, such as single-vehicle accident, leaving the roadway, or “at fault”.
    - Anticholinergic effects
        - Memory difficulty, dry mouth, constipation, hallucinations, urinary hesitation, sedation, vision changes

7.2.1 Physical Examinations

The 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.

7.2.2 Vital Signs

Assessment of vital signs (seated blood pressure, pulse rate, body temperature, respiratory rate) will be performed at the time points indicated in the SoA.

Vital signs will be measured at all visits in a seated position after 5 minutes rest and will include temperature, respiratory rate, systolic and diastolic blood pressure performed using automated blood pressure device, 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, with patient seated with arm on table or similar support at the level of chest.

The method used to measure body temperature at screening should be maintained throughout the study for each participant, and should be indicated (e.g., ear, mouth, armpit).

7.2.3 Electrocardiograms

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 supine position after the participant has rested in this position for at least 1 minute.

7.2.4 Clinical Safety Laboratory Assessments

Refer to Section 9.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The Investigator must review the laboratory report and document this review. The laboratory reports must be filed with the source documents.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from laboratory assessments not specified in the protocol and performed at the institution’s local laboratory result in the need for a change in participant management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded in the eCRF.

7.3 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 3.
Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).
The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following AEs until resolved or deemed stable.

7.3.1 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.

7.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Once an AE/SAE is reported, questioning should be directed at characterizing and documenting the event, including specific signs or symptoms not volunteered by the participant (e.g., pertinent negatives).

7.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. Participants must be proactively questioned about changes in ongoing AEs/SAEs at intervals and with a precision that is clinically appropriate for the specific AE/SAE, including documentation of duration, time or date of resolution, or change in severity or seriousness or related events. All AE/SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 3.

7.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours, see Appendix 3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC/DMC, if appropriate and according to local requirements.

7.3.5 Pregnancy

Details of all pregnancies in female participants after the start of study treatment and until at least 5 terminal half-lives after the last dose will be collected.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

7.4 Treatment of Overdose

For this study, any dose of aroxybutynin greater than 2.5 mg or of atomoxetine greater than 75 mg, more frequently than QHS will be considered an overdose.
In the event of an overdose, the Investigator should refer to the Investigator's Brochure for advice on overdose and:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until aroxybutynin and/or atomoxetine are no longer expected to be present systemically.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

8 Statistical Considerations

Statistical analysis of the study will be based on a more technical and detailed elaboration of statistical procedures, including planned analyses, population definitions and methodology presented in a Statistical Analysis Plan (SAP) that takes precedence over such descriptions in the protocol.

8.1 Sample Size Determination

The sample size has been selected based on the number of participants required to provide at least 90% power for the primary endpoint (change from baseline to week 26 in AHI4) and the key symptom secondary endpoint (change from baseline to week 26 in PROMIS Fatigue T-score).

In the previously conducted Phase 2 Mariposa study, the standard deviation of the placebo group change from baseline in AHI4 was approximately 9.0. Based on the observed dropout rates in Mariposa, it is assumed that the dropout rate in the placebo group will be 5% and the dropout rate in the AD109 group will be 25%. For the primary analysis, missing data will be handled under a missing not at random assumption by using multiple imputation from the control group. Based on the assumed standard deviation, anticipated dropout rates and planned method of handling missing data, the required sample size was estimated using simulation. A total of 640 participants (320/group) will provide >98% power to detect a treatment difference of >= 4 points between AD109 and Placebo for the change in AHI4.

In the Phase 2 Mariposa study, the standard deviation of the placebo group change from baseline in PROMIS Fatigue T-score was 8.6. Based on the observed dropout rates in Mariposa, it is assumed that the dropout rate in the placebo group will be 5% and the dropout rate in the AD109 group will be 25%. For the primary analysis, missing data will be handled under a missing not at random assumption by using multiple imputation from the control group. Based on the assumed standard deviation, anticipated dropout rates and planned method of handling missing data, the required sample size was estimated using simulation. A total of 640 participants (320/group) will provide ~90% power to detect a treatment difference of 2.5 points and ~95% power to detect a treatment difference of 2.75 points.

Based on the above a total sample size of approximately 640 participants (320/group) is planned.

8.2 Populations for Analyses

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

Set	Description
Screened	All participants who signed the ICF, including screen failures
Enrolled	All participants who signed the ICF and meet all eligibility criteria
Full Analysis Set (FAS)	All participants who were randomized. Participants will be analyzed for efficacy according to the treatment group into which they are randomized.
Safety Set	The Safety Population consists of all participants who receive at least 1 dose of any of the study treatments. Participants will be analyzed for safety based on the treatment received.
Per Protocol (PP) Set	The PP Population consists of all participants without important protocol deviations or violations that could influence efficacy assessment. Participants in this population will be analyzed according to the treatment they actually received.

8.3 Efficacy Analyses

The primary clinical question of interest is: what is the treatment effect of AD109 compared with placebo in participants with mild to severe OSA, with respect to change from baseline in AHI4 at week 26 (primary endpoint) and all secondary endpoints defined on a continuous scale, regardless of adherence to investigational product and irrespective of any changes in background therapy?

- Treatment condition: investigational treatment with AD109/Placebo regardless of adherence to investigational product and of any changes in background therapy (treatment policy strategy).
- Variable/endpoint:
  - Primary: change from baseline to week 26 in AHI4
  - Secondary:
    - Change from baseline to week 26 in ODI3, HB4, PROMIS-fatigue, PGI-S for fatigue
    - PGI-C scores at week 26
    - Change from baseline to week 26 in ESS, PROMIS sleep impairment, and exploratory endpoint AHI3a
- Population of interest: participants with mild to severe OSA
- Intercurrent events:
  - Discontinuation of study treatment prior to week 26 due to any reason is handled by the treatment condition (treatment policy strategy).
  - Change in background therapy (i.e., use of PAP or concomitant medications) is handled by the treatment condition (treatment policy strategy)
- Population-level summary measure: Difference in means between AD109 vs placebo estimated using a MMRM.

Rationale for estimand: The primary estimand aims at reflecting how participants with mild to severe OSA, are treated in clinical practice and considers both safety and efficacy.

For the key secondary endpoint of >= 50% reduction in AHI4 at week 26 the clinical question of interest is: what is the treatment effect of AD109 compared with placebo in participants with mild to severe OSA with respect to achieving at least a 50% reduction in AHI4 at week 26, irrespective of adherence to investigational product and irrespective of any changes in background therapy?

- Treatment condition: investigational treatment with AD109/Placebo regardless of any changes in background therapy.
- Variable/endpoint: Responder defined as achieving the following:
  - Achieved a ≥50% reduction from baseline in AHI4 at week 26
- Population of interest: participants with mild to severe OSA
- Intercurrent events:
  - Discontinuation of study treatment prior to week 26 due to any reason is handled by the treatment condition (treatment policy strategy).
  - Change in background therapy (i.e., use of PAP or concomitant medications) is handled by the treatment condition (treatment policy strategy).
- Population-level summary measure: Difference in response rates between AD109 vs placebo estimated using the stratified Cochran-Mantel Haenszel (CMH) approach.

Rationale for estimand: The estimand aims at reflecting how participants with mild to severe OSA, are treated in clinical practice and considers both safety/tolerability and efficacy.

The primary analysis methodology for the primary endpoint will utilize a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) in combination with the Newton Raphson Algorithm. Analyses will include treatment, AHI4 strata, time and the treatment by time interaction as fixed effects and baseline score as a covariate. An unstructured covariance matrix will be used to model the within participant error. If the model fails to converge with an unstructured covariance matrix, a compound symmetric covariance matrix will be used. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed. The Kenward-Roger approximation will be used to estimate the denominator, degrees of freedom. The lsmeans, and treatment difference in lsmeans for week 13, 26 and 51 will be reported along with the corresponding 95% confidence intervals and the p-values for the treatment group comparisons at week 13, 26 and 51. The primary comparison will be the contrast between treatment groups at week 26.

All data collected up to week 51, regardless of adherence to investigational intervention, and initiation of PAP will be used in the analysis. While every effort will be made to retain participants who discontinue investigational intervention in the trial, it is expected that there will be some missing data for a small proportion of participants. Based on a previously conducted

phase 2 study (Mariposa), we anticipate that up to 5% of placebo participants and 25% of AD109 participants may be missing their data due to early withdrawal from the trial. Given the anticipated unequal distribution of missing data between the AD109 and Placebo group, missing data will be assumed to be missing not at random (MNAR) and the endpoint will be analyzed using a pattern- mixture model using a control-based approach (further details are provided in the SAP).

Analysis of secondary endpoints that are on a continuous scale will follow the same methods as outlined for the primary endpoint. The primary analysis of the proportion of participants with ≥50% reduction in AHI4 at week 26 will utilize the Cochran-Mantel Haenszel procedure, controlling for randomization strata. An estimate of the unadjusted response rates in AD109 and placebo, the adjusted risk difference, along with the 2-sided 95% CI for the risk difference will be reported. All observed data will be used for the analysis. If there is missing data, data will be imputed using multiple imputation (further details are provided in the SAP).

To control for multiplicity, the key secondary endpoints will be tested in a fixed order if the primary endpoint is statistically significant. Further details are in the SAP.

Details of the planned supportive and sensitivity analyses, along with details of the planned analyses for additional endpoints, are provided in the SAP.

8.4 Safety and Other Analyses

Further details on the statistical analysis methods of all safety data and other data will be described in the SAP.

8.5 Interim Analyses

No interim analysis is planned.

9 Data Monitoring Committee

A Data Monitoring Committee (DMC), comprised of individuals with relevant expertise with no direct relationship to the study, will be appointed by Apnimed. The specific responsibilities of the DMC and a schedule of meetings will be described in the DMC Charter. The DMC may consider recommending early termination of the study on safety grounds.

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

9.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference on Harmonization (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 IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC guidelines, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

9.1.2 Financial Disclosure

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

9.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the signed ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

9.1.4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.1.5 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Applicable study data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory and PSG 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. 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 will be provided to study sites in a training manual. In addition, site personnel will receive training on the data capture systems.

9.1.6 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

9.1.7 Study and Site Closure

The Sponsor 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 study drug development.

9.1.8 Publication Policy

The Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

9.1.9 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.
This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the US Investigational New Drug (IND) under which the study is being conducted.
Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.1.10 Liability and Insurance

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

9.1.11 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 contract research organization (CRO) and the Sponsor of the necessary support at all times.

9.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 2 will be performed by the central laboratory.

Laboratory testing is performed non-fasting.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 2: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Platelet Count	RBC Count RBC Indices	WBC count with Differential
Serum Chemistry	Albumin BUN Creatinine Potassium Sodium Bilirubin HbA1c	ALT AST Alkaline phosphatase Calcium Magnesium Total Protein	Glucose Total cholesterol HDL cholesterol LDL cholesterol Chloride Bicarbonate Uric acid
Routine Urinalysis	Specific gravity, bilirubin, color, appearance, leukocyte esterase, nitrite, pH, protein (albumin), glucose, ketones, occult blood, urobilinogen Microscopic examination (if positive protein, leukocyte esterase, blood or nitrite)		
Other Tests	• Serum hCG pregnancy test at screening. Additional testing may be performed if needed in WOCBP. • Urine test of drugs of abuse (marijuana, cocaine, amphetamine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, propoxyphene); immunoassay with gas chromatography-mass spectrometry confirmation of positive results • 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.

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

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

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

Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow up of AE and SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. SAEs must be reported to Sponsor/designee in writing, via email, using the paper SAE Report Form, within 24 hours of becoming aware of the event. The completed paper SAE Report Form should be sent to the following email address: safetyreporting@syneoshealth.com Additionally, SAE entry into the EDC should be completed concurrent to the completion of the paper SAE Report Form. All additional follow-up evaluations of the SAE must be reported to Sponsor/designee as soon as information becomes available using the paper SAE Report Form. The Investigator will also record all relevant AE/SAE information in the eCRF. It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page and/or paper SAE Report Form. There may be instances when copies of medical records for certain cases are requested by the CRO. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the CRO. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

Follow-up of AE and SAE
The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study, the Investigator will provide the CRO with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the originally completed eCRF. The Investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information.

Reporting of SAE

SAE Reporting Via Paper SAE Report Form
The Investigator must report any SAEs to the CRO within 24 hours of becoming aware of the event. SAEs must be reported to Sponsor/designee in writing, via email, using the paper SAE Report Form, within 24 hours of becoming aware of the event. The completed paper SAE Report Form should be sent to the following email address: safetyreporting@syneoshealth.com Additionally, SAE entry into the EDC should be completed concurrent to the completion of the paper SAE Report Form. All additional follow-up evaluations of the SAE must be reported to Sponsor/designee as soon as information becomes available using the paper SAE Report Form. The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents (Investigator's Brochure or US product labeling for atomoxetine or oxybutynin). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone.

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

9.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions
WOCBP
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).
Women in the following categories are not considered WOCBP:

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

   Documented hysterectomy

   Documented bilateral salpingectomy

   Documented bilateral oophorectomy

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

3. Post-menopausal female

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to assist in determination of a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).

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 as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

Female Participants

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation Oral Intravaginal Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation Oral Injectable
Highly Effective Contraceptive Methods That Are User Independent
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation Intrauterine device (IUD) Intrauterine hormone-releasing system Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional method of contraception specified herein should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.
Double Barrier Barrier methods include use of two of the following: condom (includes external and internal); spermicides; occlusive cap (diaphragm or cervical/vault cap) with spermicide; sponge with spermicide.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive serum pregnancy test.

Pregnancy testing will be performed whenever 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 IMP treatment.

9.5 Appendix 5: List of Abbreviations

ABPM	ambulatory blood pressure monitoring
AE	adverse event
AHI	Apnea-hypopnea index
Aroxy	aroxybutynin
Ato	atomoxetine
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
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSST	digit symbol substitution test
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
IMP	investigational medicinal product
IND	investigational New Drug
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
MAOI	monoamine oxidase inhibitor

MVA	Motor vehicle accident
NREM	non-rapid eye movement
OSA	obstructive sleep apnea
OTC	over-the-counter
PAP	positive airway pressure
PGI	Patient global impression
PVT	Psychomotor vigilance test
PK	pharmacokinetic(s)
PROMIS	Patient Reported Outcome Measurement Information System
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
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential

9.6 Appendix 6: Summary of Changes

Section No. & Title	Amendment V2.0
Schedule of Activities	• Dose IMP: Added X at V3 and V8 • Footnote 14: added *includes asking about sleepiness-related motor vehicle accident (MVA)* • Abbreviations: removed *SD = Sleep Disturbance,* correction to the *Spielberger description*
Section 3 Endpoints	• Addition of PVT to Safety Objectives • Abbreviations: Addition of *PVT = psychomotor vigilance test,* correction to the *Spielberger description*
Section 4.1 Overall Design	Revised Text: *Participants who meet all eligibility criteria will be randomized to one of 2 parallel treatment arms. Enrollment will be stratified according to baseline AHI* ***(<15, 15 to 30, >30)*** *and PROMIS-Fatigue raw score* ***(<25 vs ≥25);*** *to ensure representative distribution of* ***baseline AHI severity****, the size of* ***AHI*** *strata will be controlled through enrollment limits,* ***with AHI <15 representing ~15% of patients, AHI 15to 30 representing ~70% of patients, and AHI >30 representing ~15% of patients.***
Section 4.2.1 Pre-Screening	Removed Text: ***Participants selected for screening should either have a previous history of OSA of a severity consistent with enrollment criteria based on more detailed screening questions, and have a history of either PAP intolerance or current refusal.***
Section 4.2.2 Visit 1	Added Text: *Enrolled participants are not prohibited from initiating PAP during the trial if deemed by the participant's primary care provider to be in the participant's best medical interest.* ***IMP dosing can continue if PAP is initiated.*** Revised Text: *Demographics and medical history, including medications and history of PAP use or other treatments for OSA, and confirmation of PAP* ***failure*** *or refusal.* Removed Text: ***Score of ≥ 10 on the Spielberger is exclusionary at V1.***
Section 4.2.4 Visit 3	Added Text: ***Prior to randomization confirm PAP refusal in the context of V2 PSG results.***
Section 4.2.6 Visit 4 *Section 4.2.8 Visit 5* *Section 4.2.10 Visit 6* *Section 4.2.12 Visit 7* *Section 4.2.14 Visit 8*	Added Text: *AE/SAE* ***(including sleepiness-related MVA)*** *and concomitant therapy (medication or device) monitoring*
Section 4.2.7 Contact/Call 4 *Section 4.2.9 Contact/Call 5 & 6* *Section 4.2.11 Contact/Call 7& 8*	Added Text: *The site contacts the participant on day …. for AE/SAE* ***(including sleepiness-related MVA)*** *and concomitant*

Section 4.2.13 Contact/Call 9 & 10 *Section 4.2.15 End Of Study Visit 9*	*therapy (medication or device) monitoring and review of study procedures and future study visits.*
Section 4.2.8 Visit 5 *Section 4.2.10 Visit 6*	Removed Text: ***If previously dispensed IMP is determined to be not available for dosing, the site can access replacement IMP for dosing.*** Added Text***:*** *PSG, with IMP dosing. If a participant initiated PAP during the study, the PSG is conducted without the use of PAP, and with IMP dosing* ***(if dosing not otherwise discontinued).***
Section 4.2.14 Visit 8	Added Text: *PSG, with IMP dosing. If a participant initiated PAP during the study, the PSG is conducted without the use of PAP, and with IMP dosing* ***(if dosing not otherwise discontinued).***
Section 5.1 Inclusion Criteria 4, 4a and 4b	Removed Text: *4. PAP ~~intolerance~~ failure or ~~current~~ PAP refusal.* Added Text: ***a. PAP failure is defined as no PAP use for ≥3 months prior to randomization, or return/removal of PAP device from the home.*** ***4.b. PAP refusal is defined as refusal of PAP after prior positive sleep study, or prior refusal of provider-recommended sleep study due to unwillingness to consider PAP.***
Section 5.2 Exclusion Criteria, Medical Conditions 1, 2, 4, 8, and 9	Added Text: *1. Narcolepsy, restless leg syndrome* ***requiring medication****, REM sleep behavior disorder* *8. Severe or frequent constipation* ***considered currently bothersome by the patient,*** *or symptomatic gastric motility disorder.* Revised Text: *2.* ***Current bothersome symptoms of*** *insomnia ~~disorder~~ (~~characterized by~~ difficulty initiating or maintaining sleep,* ***as distinct from unrefreshing sleep or other symptoms attributable to OSA****), ~~or use within the past month of sedative-hypnotics or other medication for the purpose of treating or avoiding insomnia symptoms~~.* ***Participants being treated for insomnia can be enrolled only if the condition is stable and generally controlled.*** *4. Clinically significant* ***or medically uncontrolled*** *cardio****vascular~~ac~~*** *disease, e.g., ventricular arrhythmia* ***requiring medical or device therapy , unstable atrial fibrillation (including cardioversion, ablation, or change in antiarrhythmic regimen within past 3 months [patients in whom anticoagulation is indicated must be on such treatment for enrollment], or resting heart rate >100),*** *untreated or unstable coronary artery disease* ***(including revascularization within 3 months)****, cardiac failure~~. Stable atrial arrhythmia is allowed~~,* ***cerebrovascular event or***

	transient ischemic attack or revascularization within 3 months. *9. Current bothersome symptoms of bladder outlet obstruction including difficulty initiating or maintaining urinary flow, straining, or sensation of incomplete bladder emptying; participants being treated with alpha-1 adrenergic antagonist for benign prostatic hypertrophy can be enrolled only if the condition is stable and generally* ***controlled****~~asymptomatic~~.*
Section 5.2 Exclusion Criteria, Diagnostic Assessments 20-29, 31	Removed and Added Text: *~~20. Score of ≥10 on the Spielberger~~* *20. MADRS-S suicidal ideation response of thinking of or planning suicide* ***(score ≥ 2)*** *Numbers revised 20-28* Added Text: ***29. History of sleepiness-related MVA.*** *31. Any condition that in the investigator's opinion would present an unreasonable risk to the participant,* ***including nature or severity of OSA symptoms****, or which would interfere with their participation in the study or confound study interpretation.*
Section 6.1 Study Drug(s) Administered	Added Text: *Study drug is taken* ***at home*** *within 30 minutes of lights out,****and taken on PSG nights at the approximate time of lights out,*** *and consists of 1 tablet. The following formulations are used in this study (as described in Section 4.1):* ***Dosing in the fully fasted state is not recommended; participants should avoid going to bed feeling hungry. A meal or snack no more than 3 hours prior to dosing is recommended.***
Section 6.4 Concomitant Therapy	Added Text: *consideration will be given to whether IMP dosing* ***and/or other study activities*** *will be temporarily paused in such circumstance.* Revised Text: • *Norepinephrine Reuptake Inhibitors (e.g.* ***atomoxetine****,* ***~~duloxetine,~~*** *reboxetine, viloxazine)* • ***~~Weight loss~~*** *Drugs* ***when used primarily or exclusively for weight loss*** *(e.g., bupropion-naltrexone, liraglutide* ***[Saxenda®]****, semaglutide* ***[Wegovy®],*** *orlistat, phentermine-topiramate)* Added Text: • *Antidiabetics****, including those that are associated with weight loss, such as GLP-1 agonists and SGLT-2 inhibitors, when used principally for the control of diabetes***
Section 6.5 Discontinuation of Study Treatment	Added Text: *If a clinically significant finding is identified, the Investigator or qualified designee will determine if IMP dosing can continue and whether any change in participant management is needed.* ***IMP dosing, and/or other associated study***

	activities, can be temporarily stopped and restarted to assess relationship of clinical findings to IMP, with prior agreement of Sponsor. ***IMP dosing can continue if PAP is initiated and no IMP stopping criteria have been met.***
Section 6.6.1 Individual Participant IMP Stopping Criteria	Revised Text: • *Blood pressure or pulse increase that, in the judgement of the investigator,* ***may be related to IMP and*** *presents a safety risk to the individual participant considering baseline factors and comorbidities. The following values* ***should be factored into a decision to*** ~~*would typically lead to*~~ *discontinue* ~~*ation of*~~ *IMP* ~~*if the measurements are considered accurate*~~*:* • *Pulse increase*~~*s*~~ *of greater than 15* ***bpm that results in an overall bpm to over 90;*** *or pulse greater than* ***100 bpm*** ~~*15*~~ Added Text: *Note that new or increased antihypertensive therapy is not itself a criterion for stopping IMP.* ***Compliance with antihypertensive therapy can be encouraged and factored into clinical decisions about IMP continuation.*** Revised Text: • *SAE considered* ~~*possibly*~~ *related* ~~*or related*~~ *to study drug.* Added Text: • ***Sleepiness-related MVA*** • *Any other AE* ***or change in participant status*** *that in the judgment of the Investigator necessitates the participant stopping IMP to protect participant safety* ***or the safety of others****.* *Participants* ***who*** *discontinue*~~*d*~~ *from dosing IMP will be encouraged to continue all other study procedures through the end of the study.*
6.7 Participant Discontinuation/Withdrawal from the Study	Removed text: *6.7 Participant* ~~*Discontinuation/*~~*Withdrawal from the Study* Revised and Added Text: *A participant may withdraw from the study at any time at his/her own request.* ***An investigator may ask a subject whether the subject wishes to provide continued follow-up and further data collection separately from interventional aspects of the study.*** ~~*Participants who withdraw from the study are requested to return for Visit 9/EOS activities approximately 2 weeks following cessation of IMP dosing.*~~ ***Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information. Participants who withdraw from the study are***

	requested to return for Visit 9/EOS activities approximately 2 weeks following cessation of IMP dosing. Revised Text: ***If a participant withdraws*** ~~*Participation may be terminated*~~ *before completing the study* ~~***and***~~ *the reason* ***should be*** *recorded to categories including the following:*
7 Study Assessments and Procedures	Revised Text: • *MADRS-S (Montgomery-Asberg depression rating scale) is a* ***nine***~~*ten*~~*-item diagnostic questionnaire* ***typically*** *used to measure the severity of depressive symptoms. Each item is based on a* ***3***~~*6*~~*-point scale, with the overall score ranging from 0-****27***~~*60*~~*. Higher scores* ***can*** *indicate more severe depression* ***or, in the context of this study, symptoms of OSA or effects of study drug.*** • *Spielberger* ~~*State-Trait*~~ *Anxiety Inventory (STAI) - short form, is a self-completed questionnaire that aims to assess* ~~*separately*~~ *state anxiety (a temporary state influenced by the current situation where the respondent notes how he/she feels right now at this moment).* ~~*And trait anxiety (a general propensity to be anxious where the respondent.*~~
7.1.1Polysomnography	Revised Numbering: ~~*7.1.1*~~ ***7.1*** *Polysomnography*
7.2 Safety Assessments	Revised Text: o *Motor vehicle accidents*~~*, "near misses," "moving violations"*~~ ♣ *Include* ***whether participant felt sleepy proximate to the MVA, and other details that may inform cause, such as*** *single-vehicle accident*~~*s*~~*,* ***leaving the roadway, or*** ~~*and violation warnings (verbal or written) and include regardless of*~~ *"at fault"* ~~*determination but include such determination if known*~~*.*
7.2.2 Vital Signs	Added Text: *Systolic and diastolic blood pressure will be repeated for a total of 3 measurements, each at least 2 minutes apart,* ***with patient seated with arm on table or similar support at the level of chest.***
7.2.4 Clinical Safety Laboratory Assessments	Revised Text: *Refer to Section* ***9.2***~~*8.*~~*2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.*
7.4 Treatment of Overdose	Removed Text: ~~*3.*~~***2.*** ~~*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).*~~
8.2 Populations for Analyses	Revised Text:

Per Protocol (PP) Set	*The PP Population consists of all participants without* ***important*** ~~*any major*~~ *protocol* ***deviations or violations*** ~~*violations*~~ *that could influence efficacy assessment. Participants in this population will be analyzed according to the treatment they actually received.*
8.3 Efficacy Analyses	Revised Text: *The primary estimand* ***is based on AHI response, irrespective of IMP compliance, use of CPAP, or any other intercurrent treatment.*** ~~*Assumes that if the participant initiated PAO and/or discontinued the study treatment, the participant is not considered a responder to study treatment. Therefore, being a responder requires a positive response, completing treatment up to week 26, and not initiating PAP prior to week 26.*~~
9.1.10.1 Access to Source Data	Revised Numbering: ~~*9.1.10.1*~~***9.1.11*** *Access to Source Data*
Table 2: Protocol-Required Safety Laboratory Assessments *Serum Chemistry* *Other Tests*	Added Text: *Albumin ALT Glucose* *BUN AST Total cholesterol* *Creatinine Alkaline phosphatase* ***HDL cholesterol*** *Potassium Calcium* ***LDL cholesterol*** *Sodium Magnesium Chloride* *Bilirubin Total Protein Bicarbonate* ***HbA1c*** *Uric acid* Removed Text: • ~~*HbA1c (Screening Visit only)*~~ Added Text: • *Urine test of drugs of abuse (marijuana, cocaine, amphetamine, methamphetamine, opiates, phencyclidine,* ***barbiturates, benzodiazepines, propoxyphene****); immunoassay with gas chromatography-mass spectrometry confirmation of positive results*
9.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information *Female participants who become pregnant*	Revised Text: *Any female participant who becomes pregnant while participating in the study will be withdrawn from* ***IMP treatment***~~*the study*~~*.*
9.5 Appendix 5: List of Abbreviations	Added Text: ***MVA Motor vehicle accident***
Section No. & Title	**Amendment V3.0**
Section 4.1 Overall Design	Added Text: *A screening/baseline PSG is conducted at V2 and is read by the central PSG reading center. For enrollment the AHI4 (hypopneas defined by 4% oxygen desaturation) of the V2 PSG must be >5* ***and ≤45****, with ≤ 25% central or mixed apneas (as proportion of total apneas + hypopneas), and PLM arousal index ≤15.*

	Revised Text: *Participants who meet all eligibility criteria will be randomized to one of 2 parallel treatment arms. Enrollment will be stratified according to baseline AHI (<15, 15 to 30, >30) and PROMIS-Fatigue raw score (<25 vs ≥25); to ensure representative distribution of baseline AHI severity, the size of AHI strata will be controlled through enrollment limits, with AHI <15 representing ~~15%~~ **~20-40%** of patients, AHI 15 to 30 representing ~~15%~~ **~20-40%** of patients, and AHI >30 representing ~~15%~~ **~20-40%** of patients.*
Section 5.1 Inclusion Criteria	Added Text: *2 PSG criteria (collected at Visit 2)* a. *AHI4 (Hypopnea defined by 4% oxygen desaturation) of >5* ***and <45.***
Section No. & Title	**Amendment V4.0**
Section 3 Endpoints *Section 8.1 Sample Size Determination* *Section 8.3 Efficacy Analysis*	*The order of endpoints, including the primary endpoint and key secondary endpoints, was changed to align with recent regulatory approvals for the treatment of OSA related to obesity.*
Section 9.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting • *Recording and follow-up of AE and SAE* • *Reporting of SAE*	*Appendix 3 updated per the protocol clarification letter v1.0 dated 17Jul2024 that clarified the process of Serious Adverse Event (SAE) reporting*

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