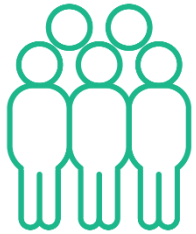
Apnimed

DRUG THERAPY FOR
OBSTRUCTIVE SLEEP APNEA

Jan 2024

Apnimed executive summary: Unique opportunity for AD109 as the first drug for the Obstructive Sleep Apnea (OSA) market

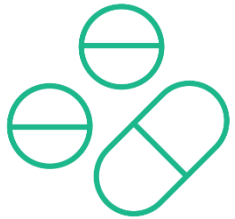


Very large market with no well-tolerated therapy

Current standard of care (CPAP) addresses the anatomical issue but not the underlying neuromuscular cause of OSA

Our oral drug AD109 addresses the neuromuscular defect

Key contributor in most patients

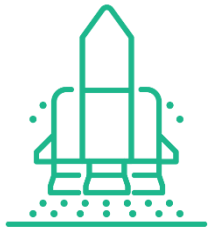


An unusual opportunity

A once-daily oral therapeutic to capture a substantial market share

AD109 Phase 3 trials in progress

Both trials currently enrolling at >120 sites in the US and Canada



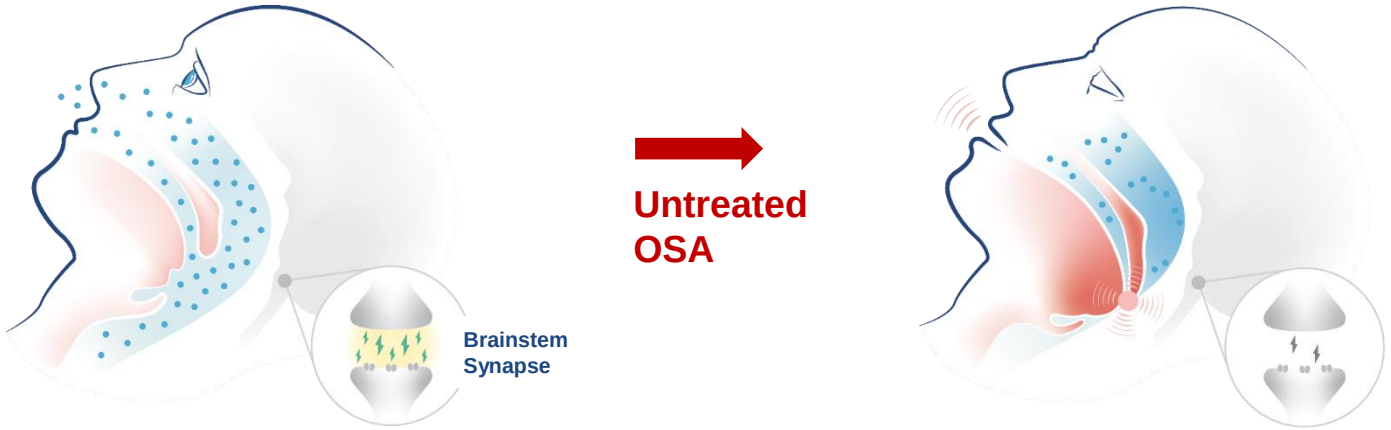
Robust Pipeline

Positive Phase 2 data for multiple follow-on candidates

AD109 NDA filing anticipated

1Q2026

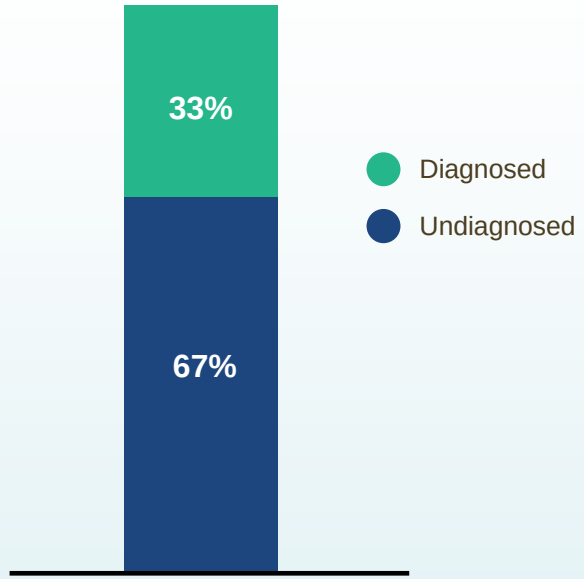
Obstructive Sleep Apnea (OSA) is a major clinical disorder (~50M in the US) with huge unmet need



OSA pathophysiology rests on a combination of narrowed upper airway and neuromuscular or ventilatory dysfunction.

These mechanisms contribute to recurrent upper airway collapse during sleep, leading to disrupted breathing and sleep fragmentation.

OSA PREVALENCE ~50 MILLION (US)



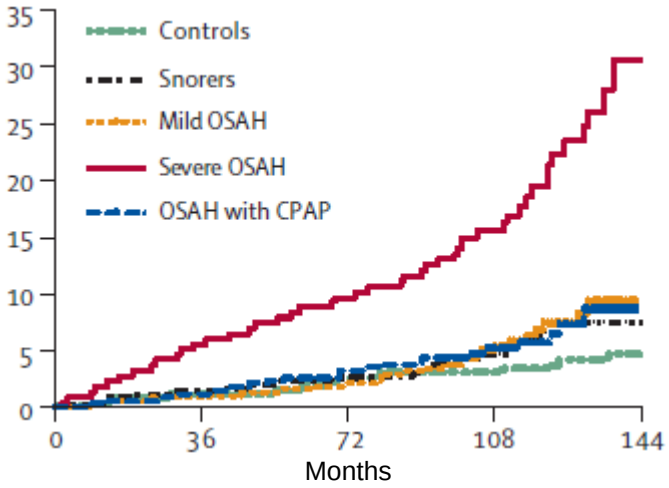
National Healthy Sleep Awareness Project, Young et al., 2009, and Frost and Sullivan, AASM, 2016, Benjafield AV et al 2019, internal Apnimed estimates

Patients with OSA are acutely symptomatic and at risk for major sequelae over time

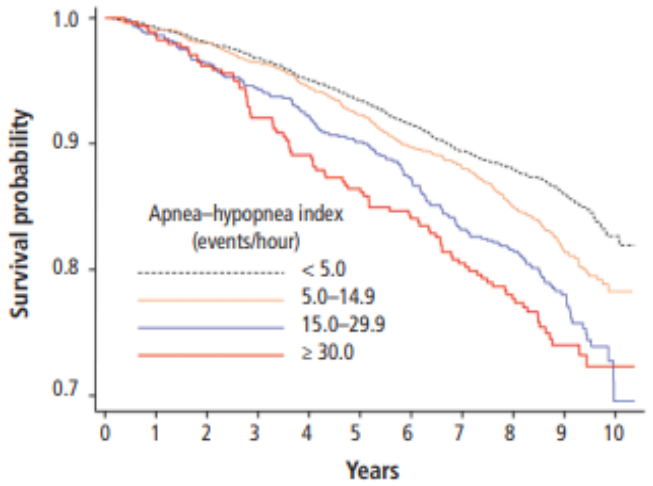
Common acute manifestations of OSA

- Daytime sleepiness
- Fatigue
- Cognitive impairment
- Loud snoring
- Dysphoria
- Motor Vehicle accidents
- Workplace accidents
- Etc.

CUMULATIVE INCIDENCE OF NON-FATAL CVS EVENTS (%)



K-M CURVE DEMONSTRATING SURVIVAL PROBABILITY (%)



Over a 12-year follow-up, patients with OSA, especially severe OSA, have a markedly increased incidence of both cardiovascular events with only partial mitigation by a compliant use of CPAP

OSA and Cardiovascular Outcomes Marin *et al* – Lancet 2005; 365: 1046–53
OSA and CD: role of the metabolic syndrome and its components. Jean-Louis G, *et al* – J Clin Sleep Med. 2008;4(3):261-272.
Punjabi NM et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009; 6(8):e100132

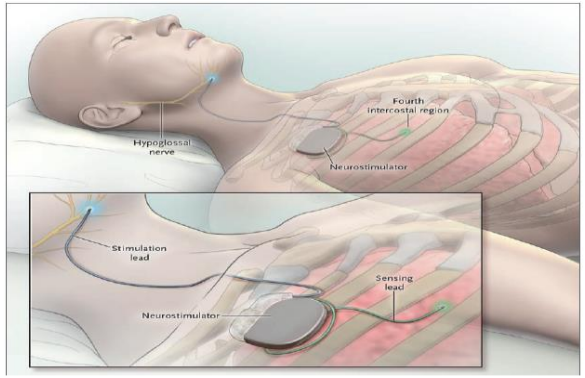
CPAP therapy is relatively unchanged over nearly 40 years: A tight-fitting mask connected to a pump

STANDARD OF CARE THERAPY

1985

Today

OTHER COMMERCIALLY AVAILABLE MEDICAL DEVICES FOR POPULATIONS WITH STRICT ELIGIBLITY CRITERIA

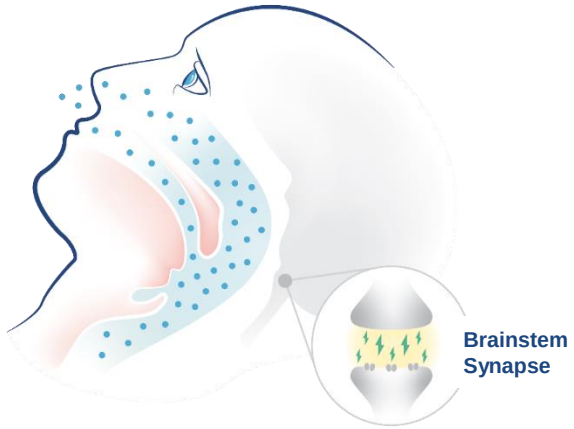


Strollo PJ et al. N Engl J Med 2014;370:139-49

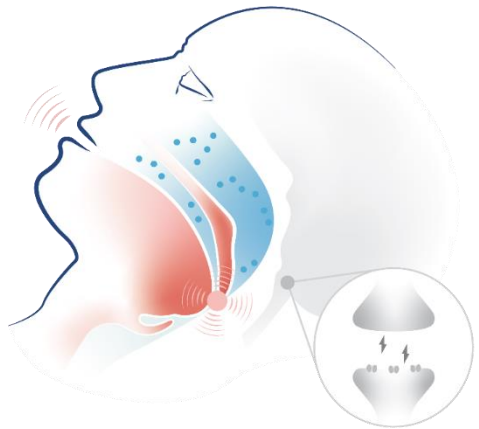
Current treatments present issues related to patient tolerance, eligibility and/or cost, but all lead to ~50% improvement in AHI.

Boyd SB, Upender R, Walters AS, Goodpaster RL, Stanley JJ, Wang L, Chandrasekhar R. Effective Apnea-Hypopnea Index ("Effective AHI"): A New Measure of Effectiveness for Positive Airway Pressure Therapy. Sleep. 2016 Nov 1;39(11):1961-1972

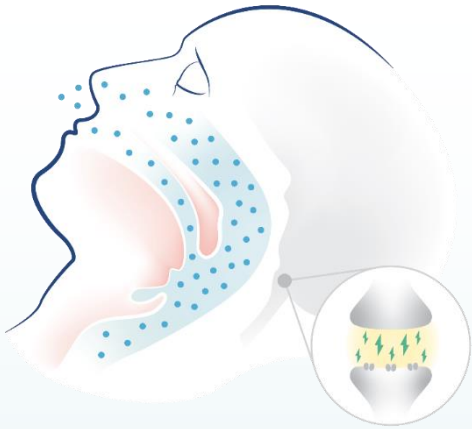
AD109 targets OSA pathophysiology by improving sleep-related reductions in upper airway muscle tone



Untreated OSA



OSA treated with AD109



Wake: Full upper airway muscle tone

CNS drives upper airway muscle dilation while awake; no obstruction even with narrow airway

Sleep: Low tone → upper airway collapse

Low CNS drive to airway dilator muscles leads to airway collapse and obstruction

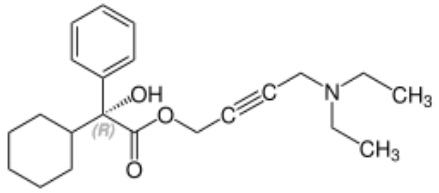
Upper airway muscle firing improves, reducing obstructions

AD109 is believed to stimulate increased firing of upper airway muscles (at the CNS level) and thus improves airflow and oxygenation

Clinical mechanism of action explored in Taranto-Montemurro, L et al. Am J Respir Crit Care Med, 2019, 199:1267-76

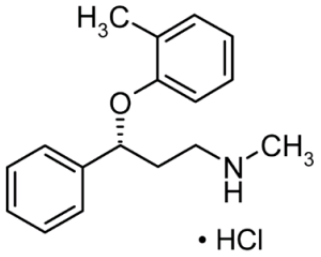
Our lead program, AD109 combines our novel antimuscarinic aroxybutynin with atomoxetine

AROXYBUTYNIN



Novel anti-muscarinic NCE, further stabilizes the upper airway and sleep

ATOMOXETINE



Selective Norepinephrine reuptake inhibitor, promotes adrenergic tone leading to muscle activation

Novel AD109 co-formulation of aroxybutynin + atomoxetine

MARIPOSA: Highly successful Phase 2b trial in ~300 pts, 1 month

MARIPOSA

STUDY RATIONALE

Confirmed efficacy over 1 month for AD109

Additional dose-finding to confirm Phase 3 dosing

Confirmed endpoints for Phase 3: AHI and PROMIS for symptoms

KEY TAKEAWAYS

Robustly positive objective and subjective efficacy for AD109 at 1 month

- Primary Endpoint met: AHI improvement
- Key Secondary Endpoints met: Improvement of OSA symptoms (PROMIS)
- Measures of sleep quality confirm clinical benefit

Confirmed Phase 3 dosing: Aroxy 2.5mg/Ato 75mg is effective and better tolerated

- AD109: Both Aroxy 2.5 and 5mg effective, lower dose superior with fewer AEs

Confirmed both drugs required for efficacy and safety, Meets FDA "combination rule"

- Aroxybutynin *required* for improved OSA symptoms, stable sleep

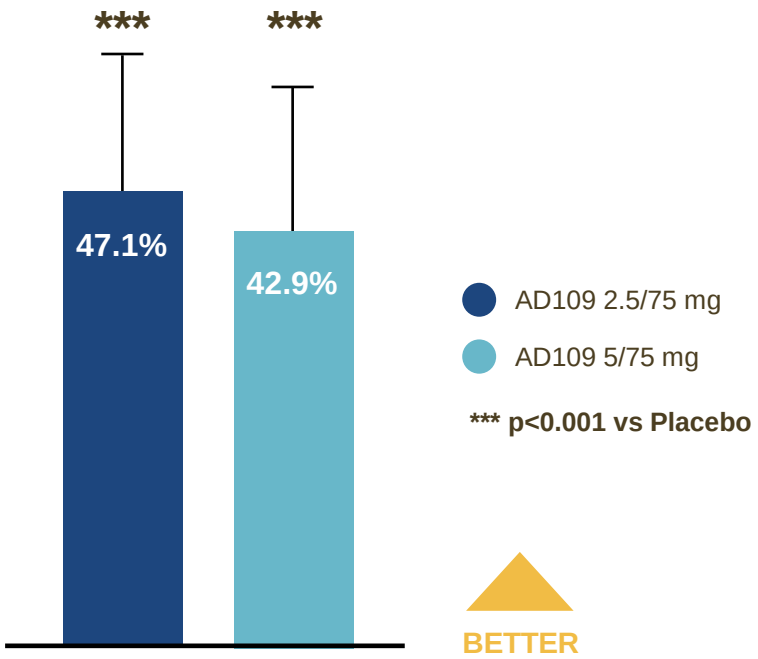
AD109 (Aroxy 2.5mg/Ato 75mg) safe and well tolerated

- All AD109 AEs mild or moderate; no Serious AEs or deaths
- No emergent AEs from AD109 when compared to observed characteristic effects of the constituent compounds

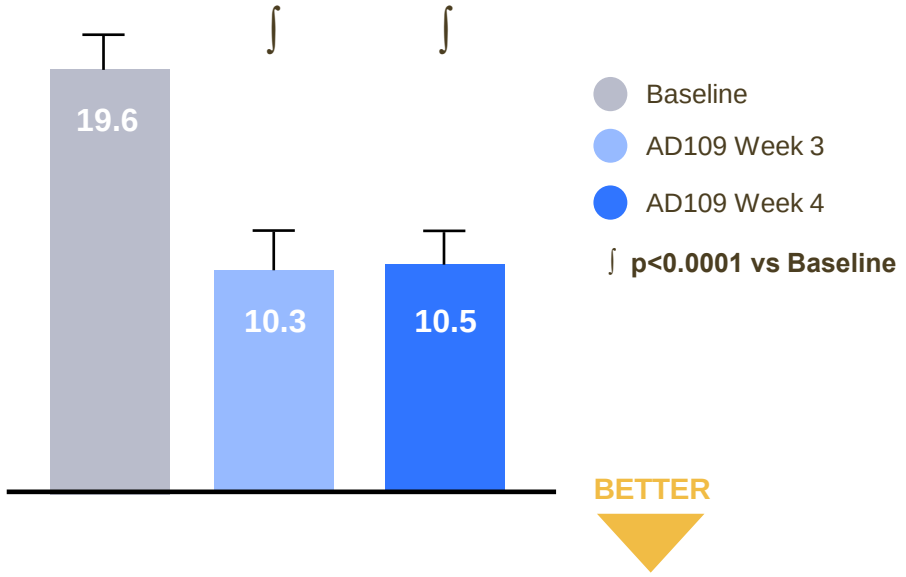
Schweitzer PK, Taranto-Montemurro L, Ojile JM, Thein SG, Drake CL, Rosenberg R, Corser B, Abaluck B, Sangal RB, Maynard J. The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2023 Dec 15;208(12):1316-1327.

AD109 robustly positive for improved airway obstruction

% REDUCTION IN APNEA-HYPOPNEA INDEX (AHI) AFTER 4 WEEKS
RELATIVE TO PLACEBO



APNEA-HYPOPNEA INDEX (AHI) FOR BOTH AD109 DOSES AT BASELINE THROUGH 4 WEEKS



AD109 vs placebo for AHI (p<0.001), with >40% reduction in AHI

Stable efficacy over 1 month: reassuring for success over longer Ph3 duration

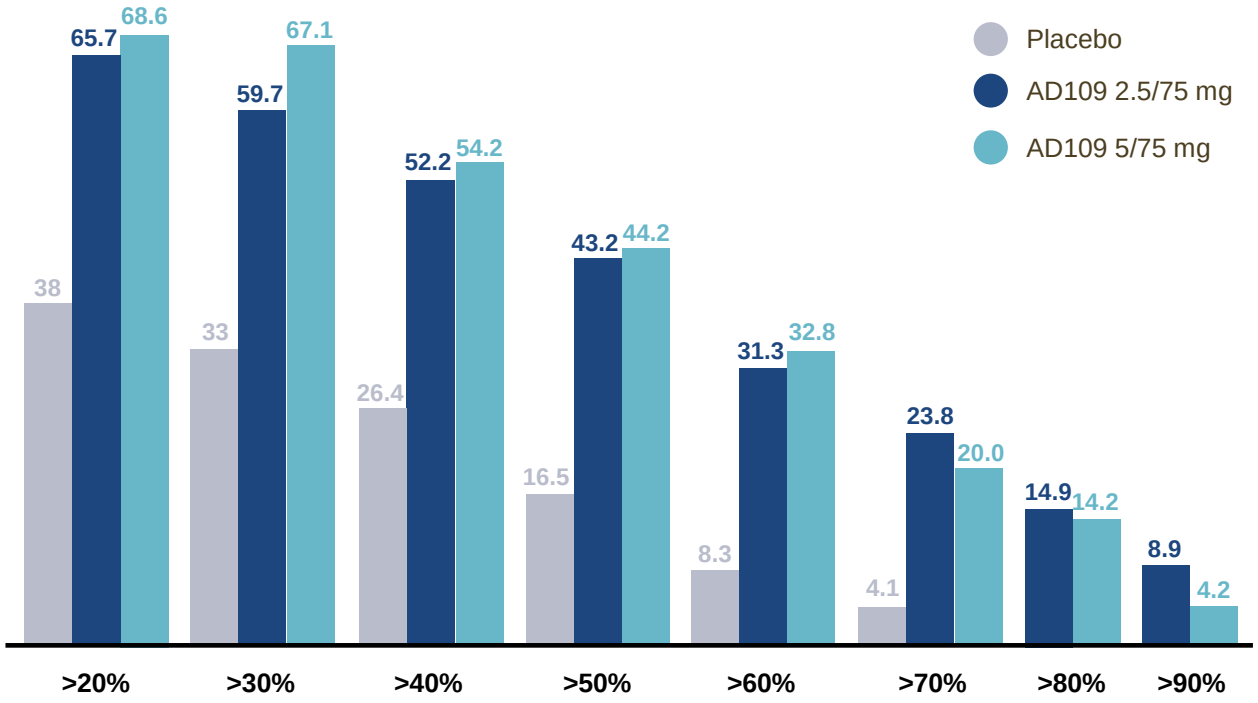
Left figure from transformed ANCOVA model and shows means (95% CI), right figure shows median (SEmedian)

Schweitzer PK, Taranto-Montemurro L, Ojile JM, Thein SG, Drake CL, Rosenberg R, Corser B, Abaluck B, Sangal RB, Maynard J. The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2023 Dec 15;208(12):1316-1327.

Most AD109 patients had robust reductions in AHI4 with 41% achieving a full clinical response

Apnea-Hypopnea Index (AHI4) Responder Analysis

PROPORTION OF PATIENTS REDUCTION IN AHI (%)



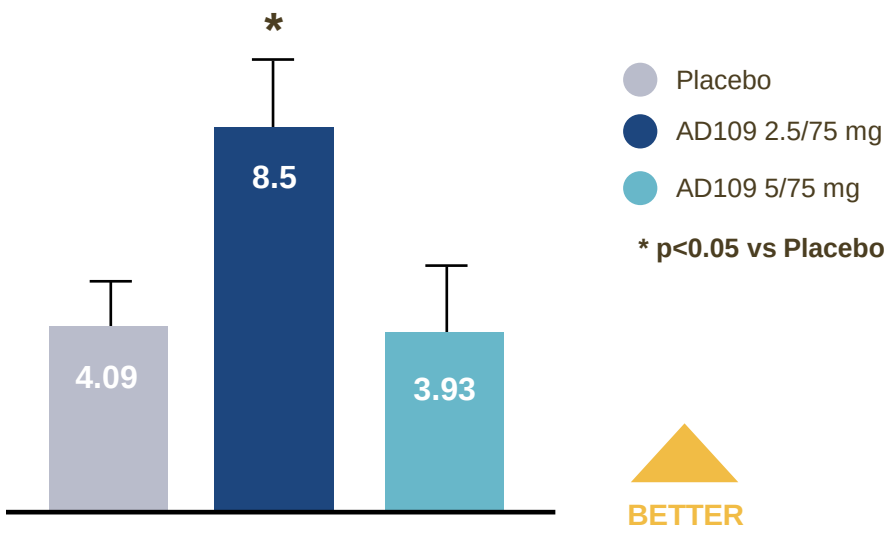
41% of all patients on the AD109 2.5/75mg dose saw their AHI4 reduced below 10

At that level of AHI reduction, no further Rx may be needed in the clinical setting.

Schweitzer PK, Taranto-Montemurro L, Ojile JM, Thein SG, Drake CL, Rosenberg R, Corser B, Abaluck B, Sangal RB, Maynard J. The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2023 Dec 15;208(12):1316-1327.

AD109 improves OSA symptoms; PROMIS-Fatigue a good Patient-reported Outcome (PRO) for Ph3

PROMIS – FATIGUE (T-SCORE)
REDUCTION RELATIVE TO BASELINE



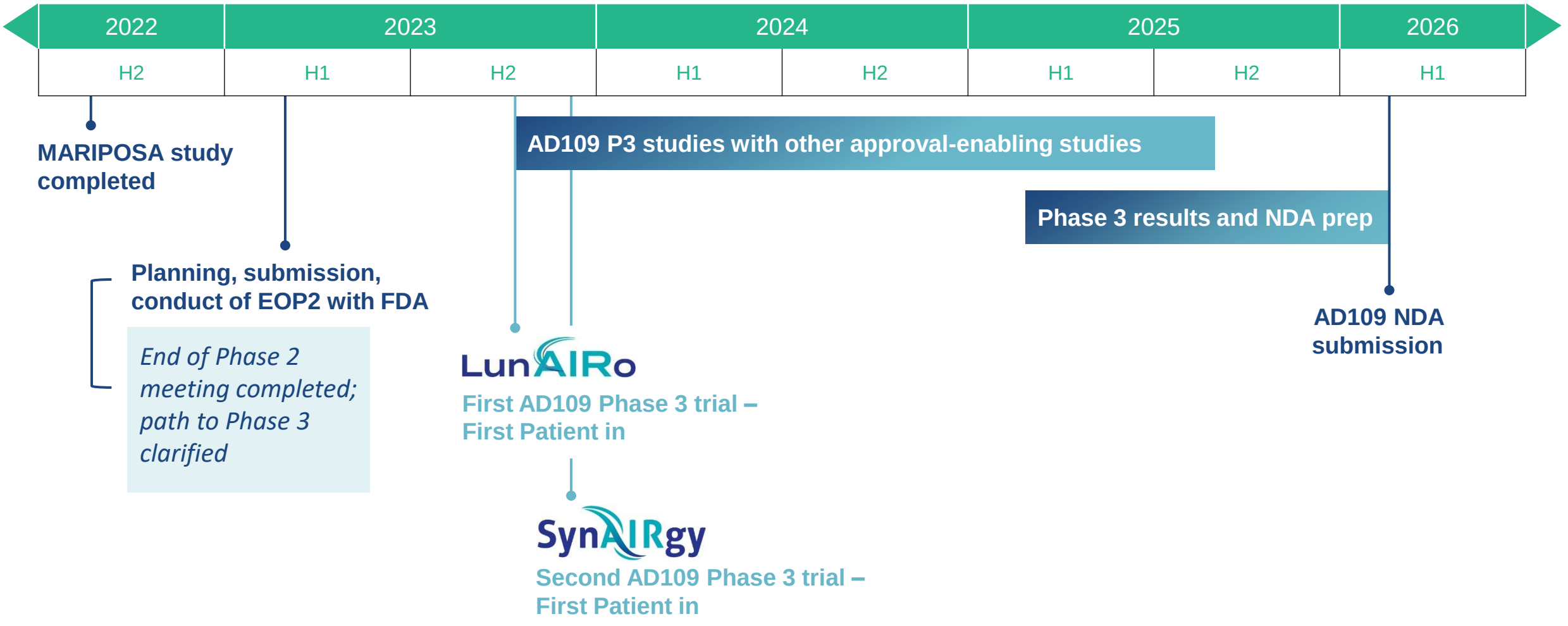
Measurement of OSA symptoms important to patients

- Fatigue can be a debilitating symptom of OSA
- PROMIS-Fatigue is a validated scale that assesses
  - Experience of fatigue
  - Interference of fatigue with daily activities
- AD109 demonstrated a statistically significant signal with a clinically-meaningful effect size
- Lower dose of aroxybutynin is superior, higher dose associated with sedation
- AD109 2.5/75 mg selected for Phase 3 program

Data represent means (SEM)

Schweitzer PK, Taranto-Montemurro L, Ojile JM, Thein SG, Drake CL, Rosenberg R, Corser B, Abaluck B, Sangal RB, Maynard J. The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2023 Dec 15;208(12):1316-1327.

AD109 path to NDA filing

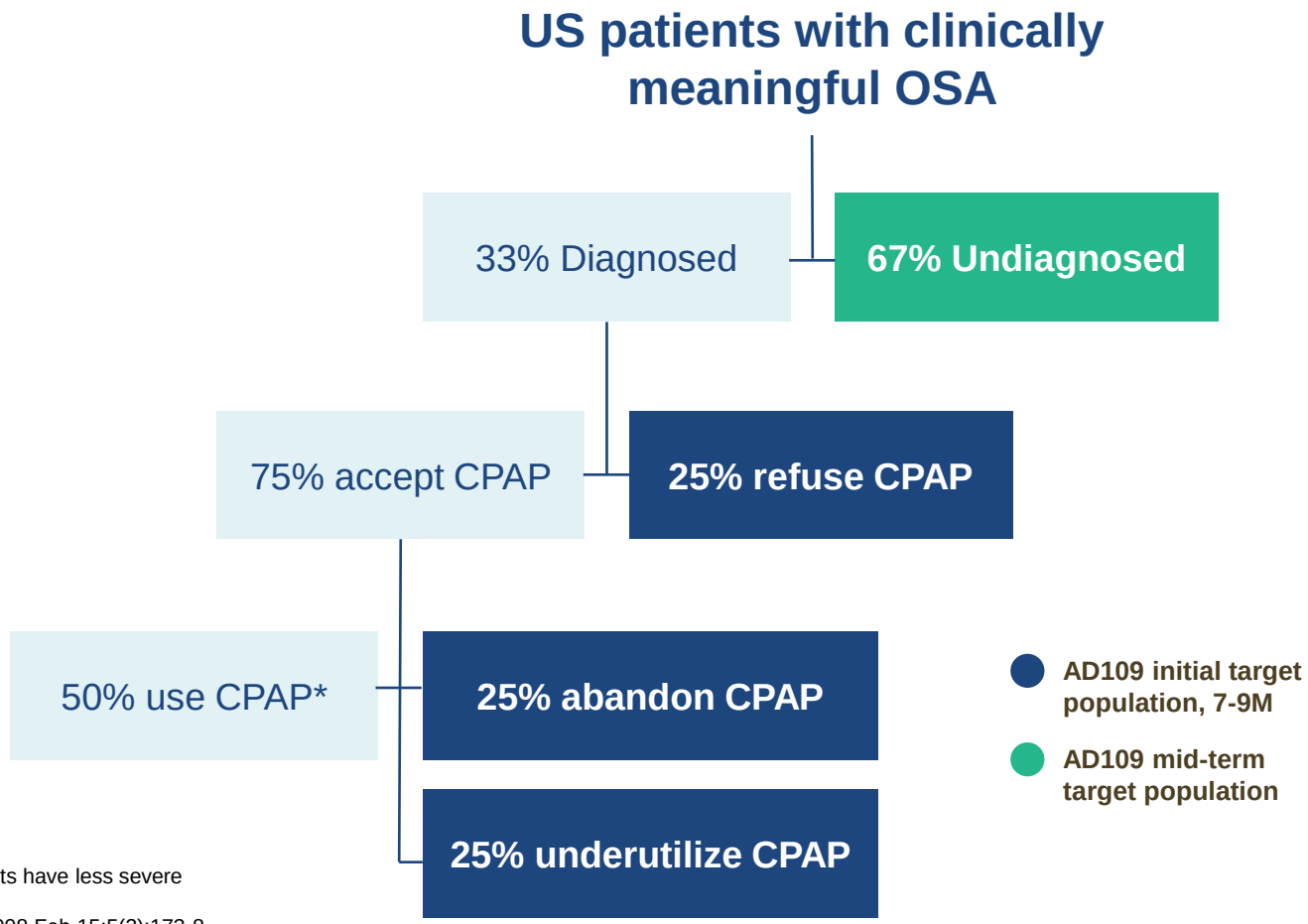


AD109 Phase 3 pivotal trials per FDA guidance

	LunAIRo	SynAIRgy
Study Design & Sample Size	• 640 participants • Randomized 1:1 to placebo vs. AD109 (aroxybutynin 2.5 mg/atomoxetine 75 mg) • 12-month dosing duration	• 640 participants in main cohort • Randomized 1:1 to placebo vs. AD109 (aroxybutynin 2.5 mg/atomoxetine 75 mg) • 6-month dosing duration • Exploratory cohort, ≤100 participants concomitantly on GLP-1 agonist for weight loss
Primary Endpoint	Reduction in AHI	Reduction in AHI
Key Secondary Endpoint	Improvement in PROMIS-Fatigue score	Improvement in PROMIS-Fatigue score
Study Population	• Adults (≥18yrs) with mild to severe OSA who decline or do not tolerate CPAP • BMI <40 in men and <42 in women	
Sites & Geographies	65 US sites	65 US & Canada sites
Initiation of Recruitment	August 2023	November 2023
Clinicaltrials.gov Identifier	NCT05811247	NCT05813275

Significant commercial potential in large US and global market

- Clinician research indicates enthusiasm for new modality
- Patient demand likely an important component
- Reasonable pricing could drive strong market access
- Amenable to therapeutic trial unlike other therapies



Clinically meaningful OSA is defined as patients with an AHI >15, or AHI>5 with symptoms. Additional patients have less severe OSA diagnoses and present potential spillover revenue opportunity
*McEvoy RD et al. N Engl J Med 2016; 375:919-931 and Weaver TE, Grunstein RR. Proc Am Thorac Soc. 2008 Feb 15;5(2):173-8

Apnimed pipeline

Program	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
AD109 (aroxybutynin+ atomoxetine)	OSA					LunAIRo SynAIRgy
AD504 / AD817	OSA with sleep disruption (novel NRI combination)					
AD113	OSA with hypertension				SHIONOGI Shionogi-Apnimed Sleep Science	
AD981	Treatment-resistant Obesity Hypoventilation Syndrome (OHS)*					
AD416	OSA (novel NRI combination)					
JV Clinical Programs	Sleep Apnea subtypes				SHIONOGI Shionogi-Apnimed Sleep Science	
JV Novel Chemistry & Targets	Sleep Apnea subtypes	SHIONOGI Shionogi-Apnimed Sleep Science				

*Tx-resistant OHS is a possible Orphan indication. Orphan Designation has not yet been evaluated or granted by FDA or other global regulatory agencies.

Powerful IP position in pharmacologic treatment of OSA

KEY FILINGS FOR LEAD CANDIDATE AD109

Method of Combining NRI + Antimuscarinic for OSA

US Patent issued, Pat. No. 11,123,313

Expires June 2038

- Broad claims for method of treating OSA and related conditions with combination of a norepinephrine reuptake inhibitor (NRI) and a muscarinic receptor antagonist
- Expected opportunity for extension of term with PTE
- Licensed from Brigham & Women's Hospital

Aroxybutynin + Atomoxetine for OSA

US Patent allowed December 2023

- Method of treating OSA and related conditions with the specific AD109 combination of aroxybutynin and atomoxetine
- Patent term to January 2039 or longer with opportunity for PTE

Novel Aroxybutynin Solid Forms

- Multiple patent families
- Expected protection beyond 2040

Extensive additional filings across other classes of compounds exemplified through exploratory study

Newly formed JV Shionogi-Apnimed Sleep Science will accelerate the development of new therapeutics for OSA

A joint venture that combines expertise

Apnimed + SHIONOGI

- Deep knowledge of OSA and clinical development of oral pharmaceuticals
- Highly experienced team for drug development
- Robust network of clinical sites for sleep disorders

- Highly efficient small molecule drug discovery engine
- Proven ability to create best-in-class compounds
- Reflects Shionogi's corporate objective to develop novel compounds in OSA

JOINT VENTURE SUMMARY

- 50/50 JV ownership; both companies contribute certain IP
- Apnimed to lead clinical development; Shionogi to lead discovery efforts
- Shionogi provides financial support for operations of the JV
- Apnimed's lead programs AD109 and AD504 are excluded from the JV
- Total transaction value of $150MM
- Both discovery and clinical programs expected to kick-off in 2024

Apnimed has a strong history backed by experienced investors

KEY LEADERSHIP

Larry Miller, MD
Chief Executive Officer

Dennis Molnar
Chief Operating Officer

Michael Rogers
Chief Financial Officer

Ron Farkas, MD, PhD
Chief Medical Officer

Luigi Taranto Montemurro, MD
Chief Scientific Officer

Graham Goodrich
Chief Commercial Officer

John Yee, MD, MPH
SVP, Medical Affairs

John Cronin, MD
SVP, Clinical Development

SELECTED INVESTORS

Alpha Wave Ventures

Columbia-Seligman

Morningside Ventures

ResMed

Sectoral Asset Management

Shionogi & Co., Ltd.

Tao Capital

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Former Chairman and CEO, Boehringer Ingelheim US

François Beaubien
Sectoral Asset Management

Dennis Molnar
Chief Operating Officer

Transformational opportunity for the first, once-daily oral drug for OSA

OSA is a serious, high-prevalence condition associated with reduced quality of life, cardiovascular disease, and early mortality; no drug therapy available

AD109 with excellent efficacy/safety in multiple Phase 2 trials, Phase 3 trials in progress

Expect data readout 2025, NDA filing and approval 2026, launch 2027

Strong IP position for AD109, extensive filings for other pharmacologic treatments


Apnimed