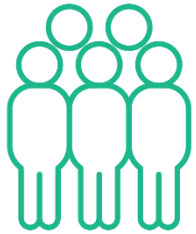
Apnimed

DRUG THERAPY FOR
OBSTRUCTIVE SLEEP APNEA

Nov 2023

Apnimed executive summary: Unique opportunity in Obstructive Sleep Apnea (OSA) market without therapeutics

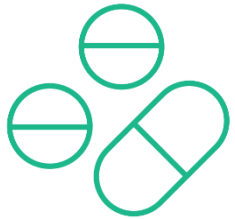


Very large market with no well-tolerated therapy

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

Our drug AD109 addresses the neuromuscular defect

AD109 is well-tolerated by patients



An unusual opportunity

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

AD109 Phase 2 trials concluded with demonstrated efficacy and safety

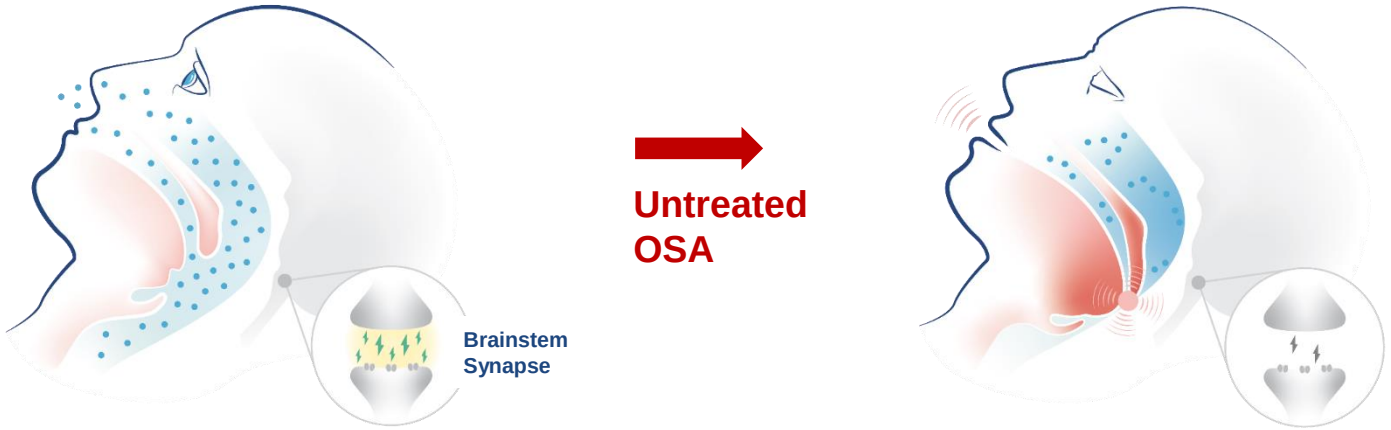
Phase 3 program began in 3Q 2023

Potential path to approval in ~ 3 years

NDA filing anticipated

2H 2025

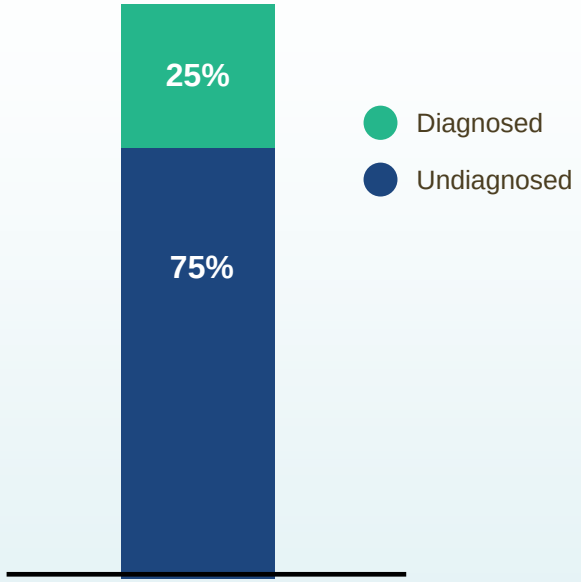
Obstructive Sleep Apnea (OSA) is a major clinical disorder (~50M in the US) with huge unmet need



OSA pathophysiology involves sleep-related obstruction due to factors like small upper airway caliber, minimal upper airway muscle response, and breathing stability.

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

OSA PREVALENCE
~50 MILLIONS (US)



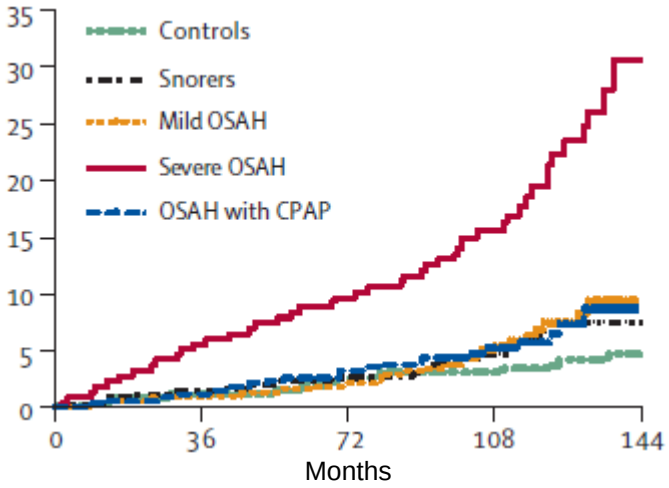
National Healthy Sleep Awareness Project, Young et al., 2009, and Frost and Sullivan, AASM, 2016, Benjafield AV et al 2019

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

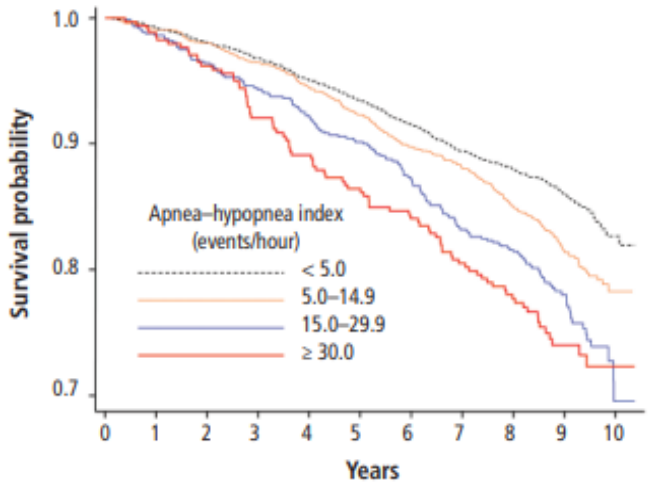
Common acute manifestations of OSA

- Daytime sleepiness
- Fatigue
- Cognitive impairment
- Loud snoring
- Dysphoria
- Auto 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

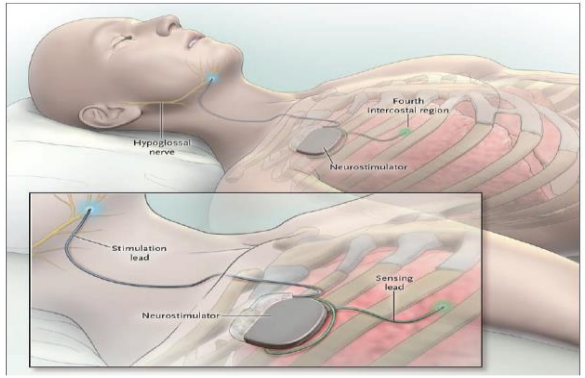
CPAP therapy is relatively unchanged over nearly 40 years: A tightly-fitted mask connected to a pump

STANDARD OF CARE THERAPY

1985

Today

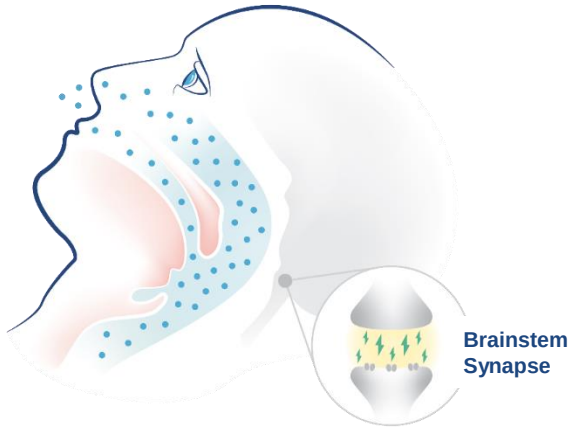
OTHER COMMERCIALLY AVAILABLE TREATMENTS FOR POPULATIONS WITH STRICT ELIGIBLITY CRITERIA



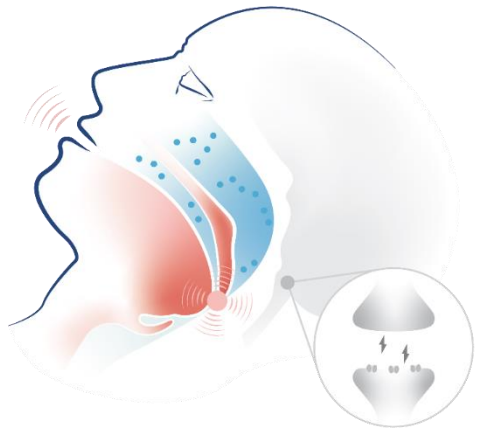
Strollo PJ et al. N Engl J Med 2014;370:139-49

All current treatments present issues related to patient tolerance, eligibility and/or cost.

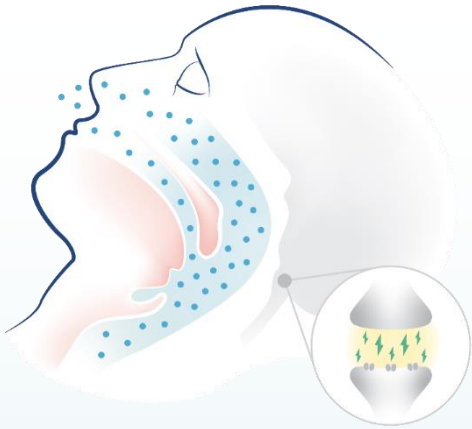
AD109 targets OSA pathophysiology by improving sleep-related reductions in upper airway muscle tone



Untreated OSA



OSA treated with AD109



Wake: Full airway muscle tone

CNS drives airway muscles while awake; no obstruction, even lying down

Sleep: Low tone → airway collapse

Low CNS drive to airway dilator muscles; combined with small/collapsible airway often related to obesity

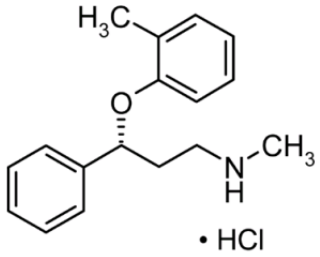
Airway muscle firing improves, reducing obstructions

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

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

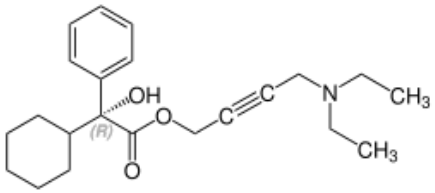
Our lead program, AD109 combines our novel antimuscarinic aroxybutynin with atomoxetine

ATOMOXETINE



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

AROXYBUTYNIN



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

Novel AD109 co-formulation of aroxybutynin + atomoxetine

MARIPOSA trial: Highly successful trial in ~300 patients, 1 month

MARIPOSA

STUDY RATIONALE

Confirm efficacy over 1 month for AD 109

Additional dose-finding to confirm Phase 3 dosing

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

- Atomoxetine alone disturbs sleep, poorly tolerated
- Aroxybutynin *required* for improved OSA symptoms, stable sleep

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

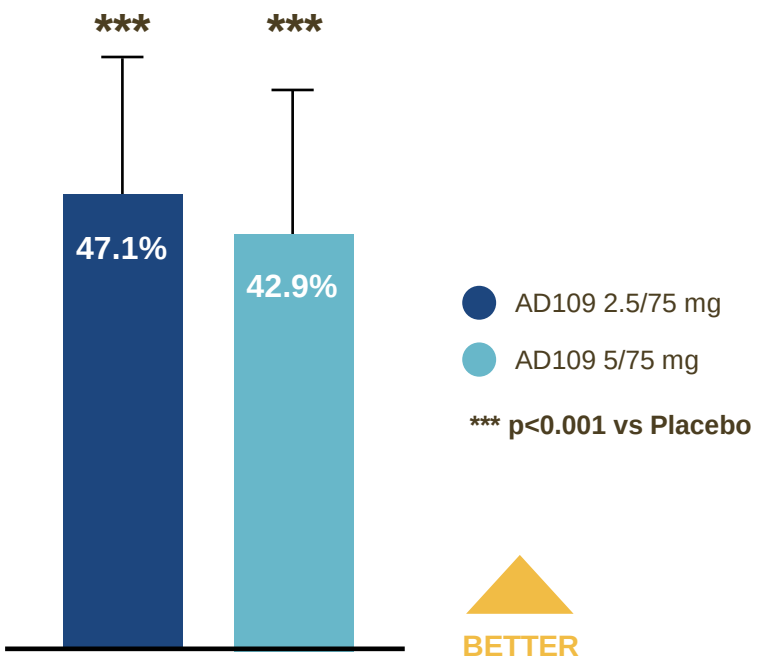
- AD109: Both Aroxy 2.5 and 5mg effective, lower dose superior with fewer AEs

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

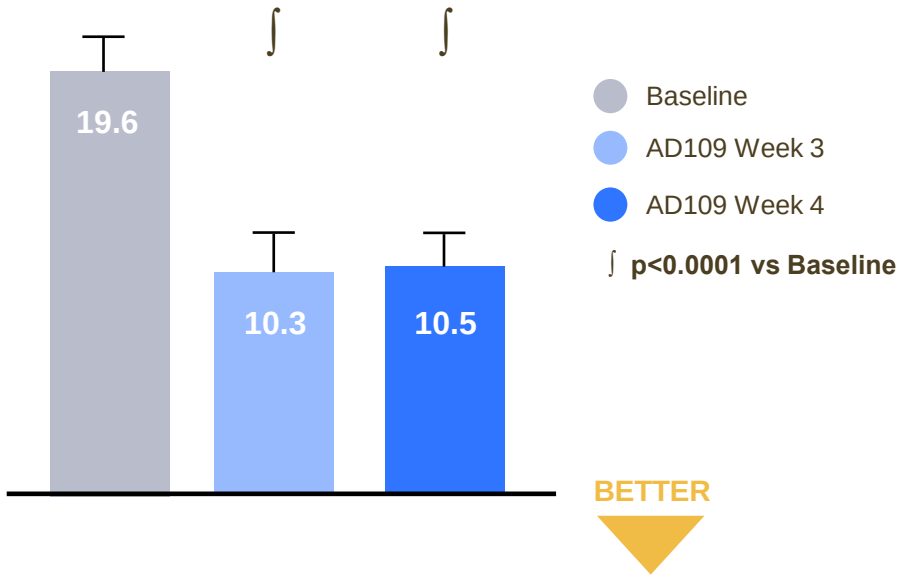
- All AD109 AEs mild or moderate
- No Serious AEs, deaths or unexpected AEs

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

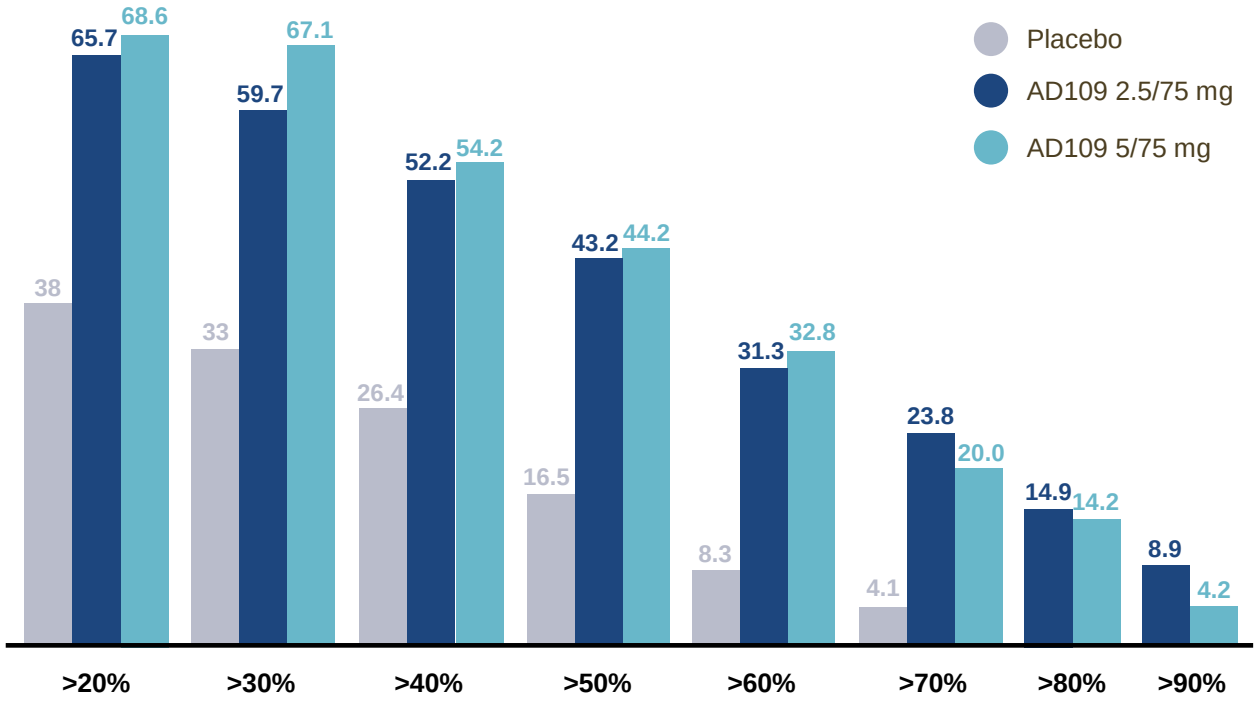
Stable efficacy over 1 month: reassuring for success over longer 3 month Ph3 duration

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

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 (%)

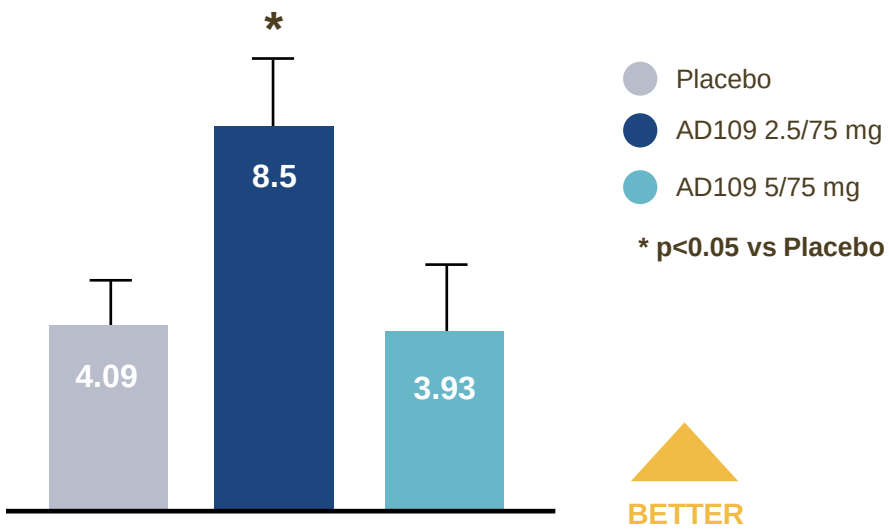


41% of all patients on the AD109 2.5/75mg dose saw their AHI4 reduced below 10

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

AD109 improves OSA symptoms; PROMIS-Fatigue a good choice for Ph3

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

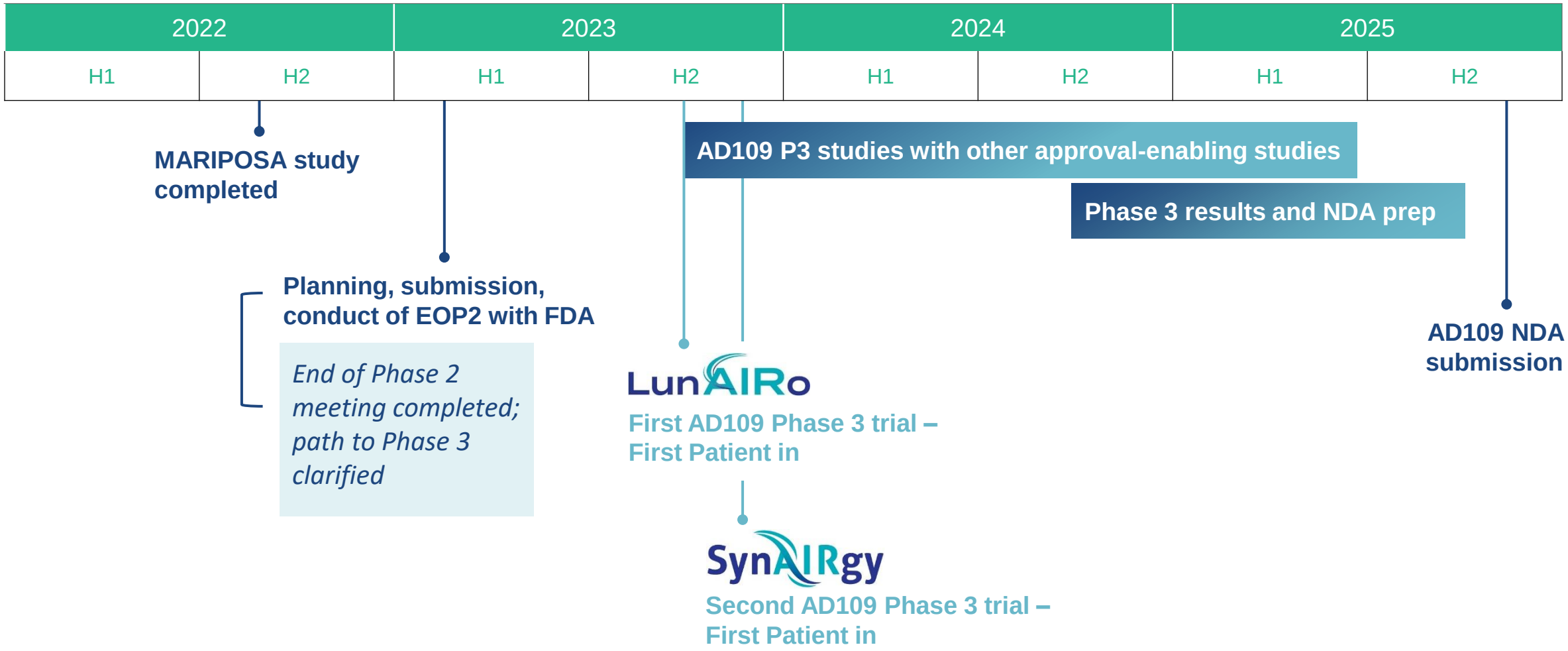


Measurement of OSA symptoms important to patients

- 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
- Successful dose finding showed an apparent difference of efficacy-tolerability balance across doses

Data represent means (SEM)

AD109 path to NDA filing

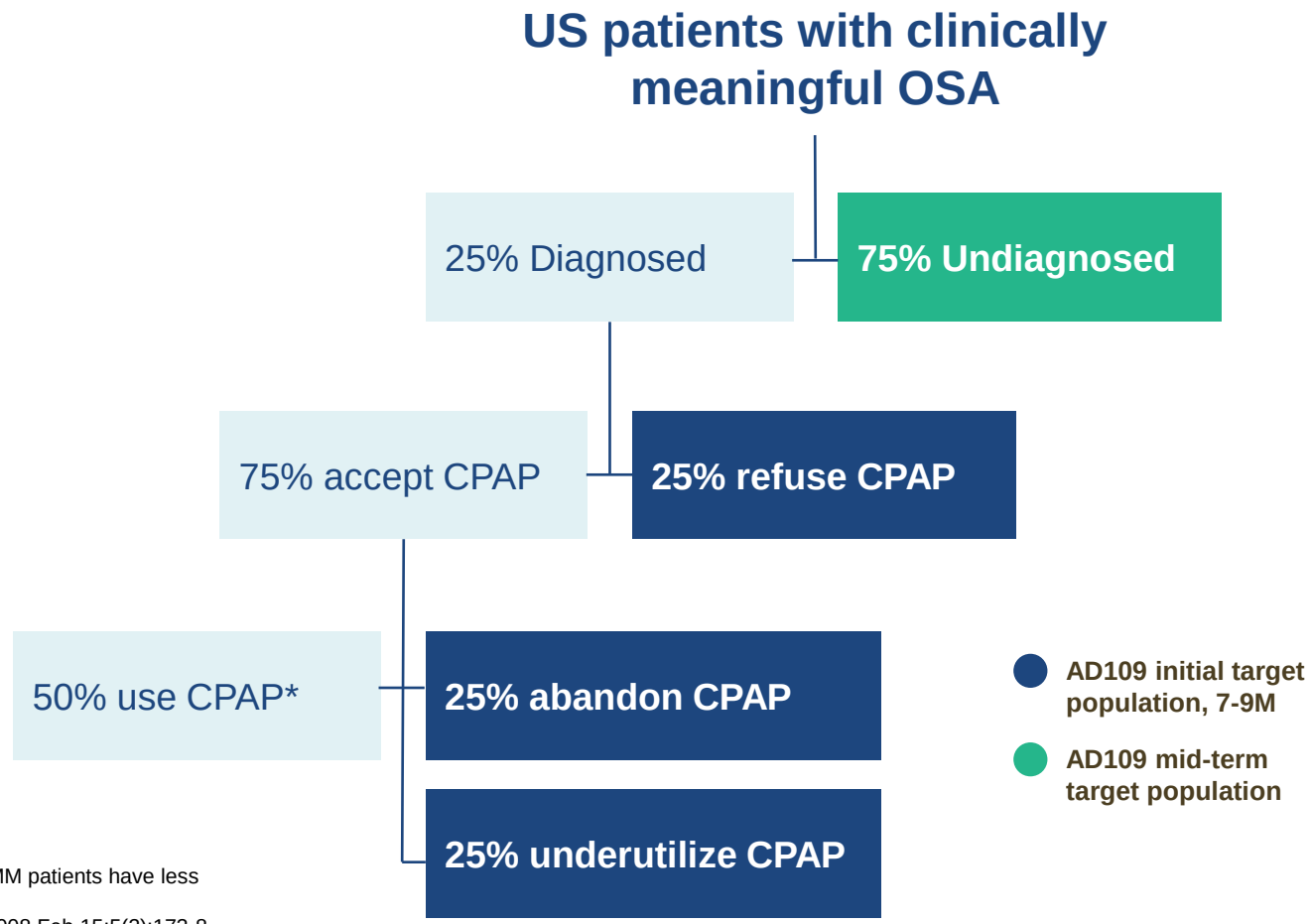


AD109 phase 3 pivotal studies

	LunAIRo	SynAIRgy
Study Design & Sample Size	640 participants Randomized 1:1 to placebo vs. AD109 12-month dosing duration	640 participants Randomized 1:1 to placebo vs. AD109 6-month dosing duration
Key Endpoints	**Primary**: reduction in AHI **Key secondary**: improvement in PROMIS-Fatigue score	**Primary**: reduction in AHI **Key secondary**: 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	4Q 2023
Clinicaltrials.gov Identifier	NCT05811247	NCT05813275

Significant commercial potential in large US and global market

- Initial marketing efforts focus on 6,000 US sleep clinicians
- Reasonable pricing could drive strong market access
- Clinician research indicates enthusiasm for new modality
- Amenable to therapeutic trial unlike other therapies



Clinically meaningful OSA is defined as patients with an AHI >15, or AHI>5 with symptoms. An additional 2MM 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

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

A joint venture that combines expertise:

Apnimed

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

+

SHIONOGI

- 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

Selected Deal Terms

- 50/50 JV ownership; both companies contribute certain IP to accelerate R&D activities
- Apnimed to lead clinical development; Shionogi to lead discovery efforts
- Shionogi provided financial support for operations of the JV
- Equity investment into Apnimed
- Apnimed's lead programs AD109 and AD504 are excluded from the JV
- Total transaction value of $150MM

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 has shown excellent efficacy and safety in multiple Phase 2 trials

Phase 3 trials began 3Q 2023 with likely NDA filing in 2025

Experienced management team and investor syndicate


Apnimed