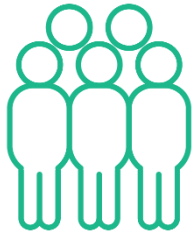
Apnimed

# DRUG THERAPY FOR **OBSTRUCTIVE SLEEP APNEA**

November 2022

# Apnimed executive summary: Unique opportunity in market without therapeutics

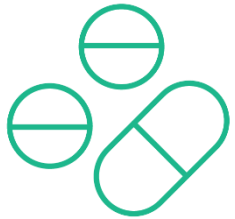


## Very large market with no well-tolerated therapy

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

Expect prompt entry to Phase 3

## Potential path to approval in ~ 3 years

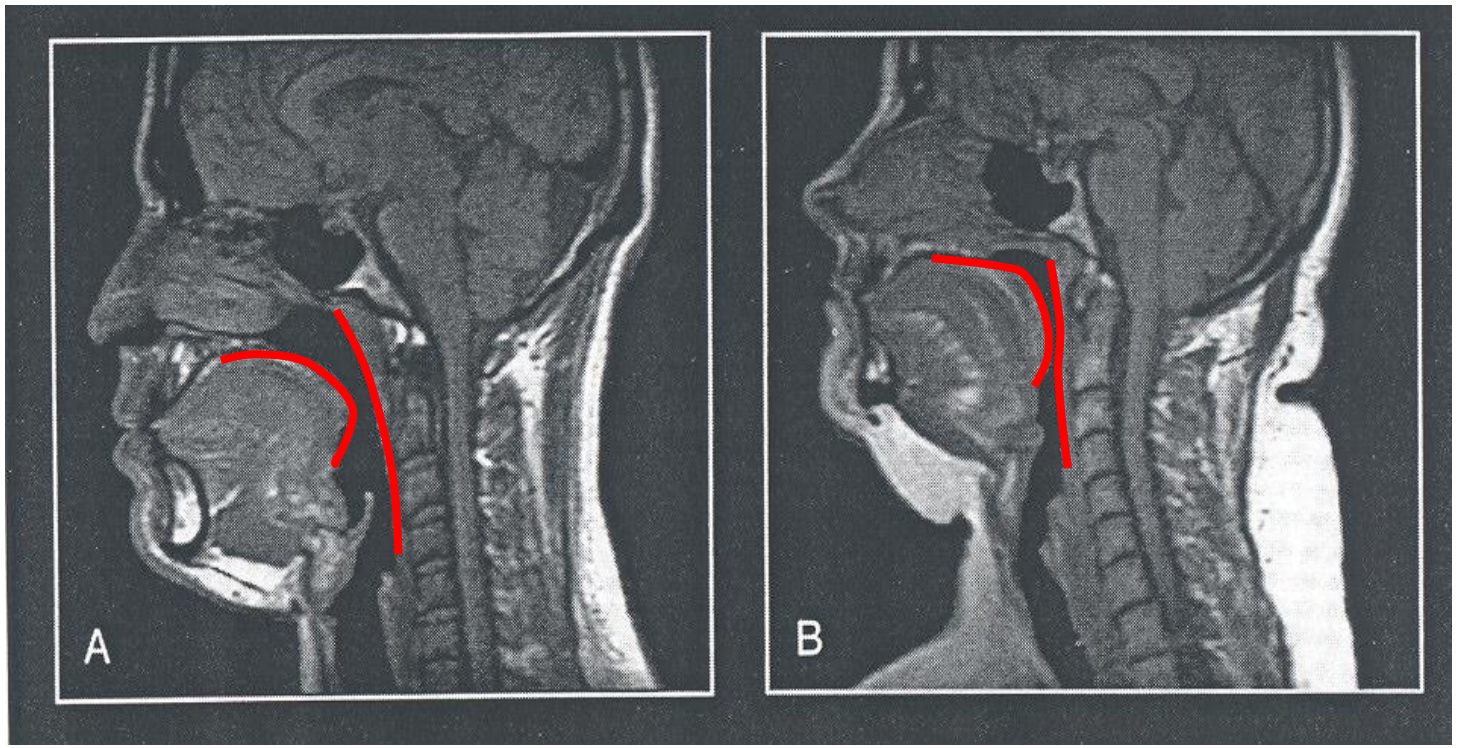
*NDA filing anticipated*

1H 2025

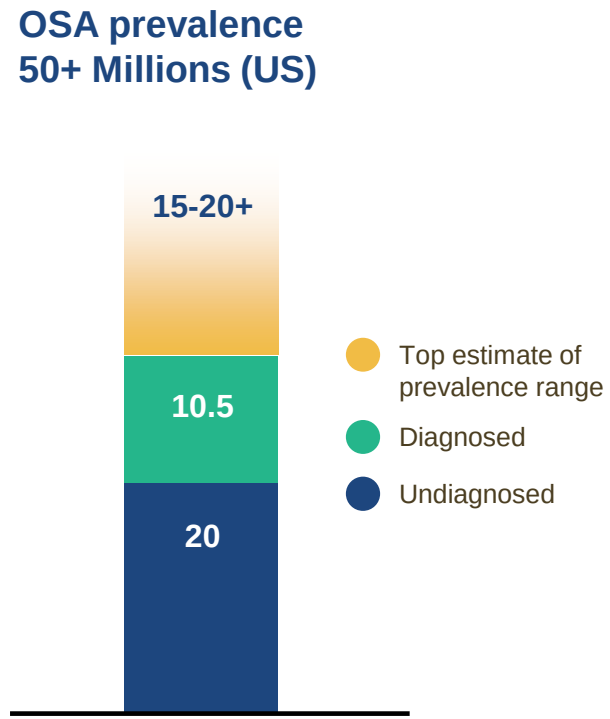
# Obstructive Sleep Apnea (OSA) is a major clinical disorder (>50M in the US) with huge unmet need

NORMAL CONTROL

OSA PATIENT




Richard Schwab, Clinics in Chest Medicine, 1998



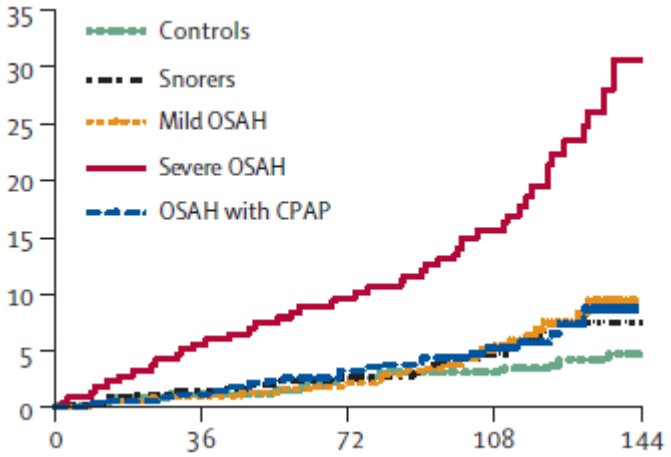

National Healthy Sleep Awareness Project, Young et al., 2009, and Frost and Sullivan, AASM, 2016, Benjafield AV et al 2019

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

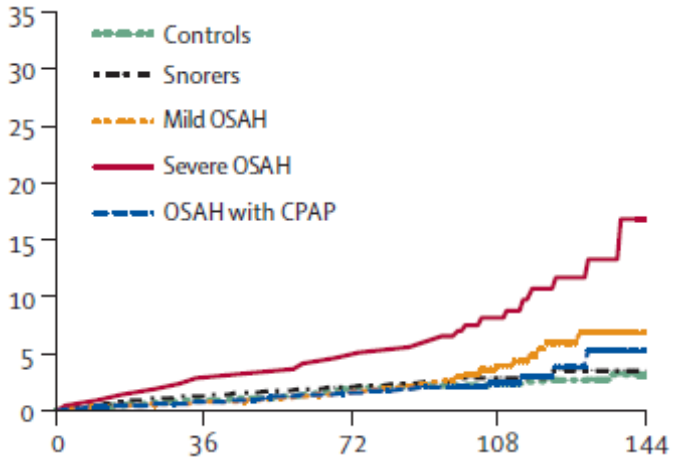
## Common acute manifestations of OSA

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

### CUMULATIVE INCIDENCE OF NON-FATAL CVS EVENTS (%)




### CUMULATIVE INCIDENCE OF FATAL CVS EVENTS (%)




*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.

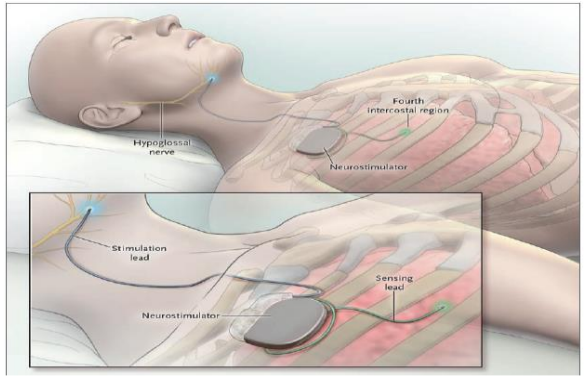
# CPAP therapy is relatively unchanged over nearly 40 years: A tightly-fitted mask connected to a pump

## STANDARD OF CARE THERAPY

**1985**


**Today**

## OTHER COMMERCIALLY AVAILABLE TREATMENTS FOR POPULATIONS WITH STRICT ELIGIBLITY CRITERIA

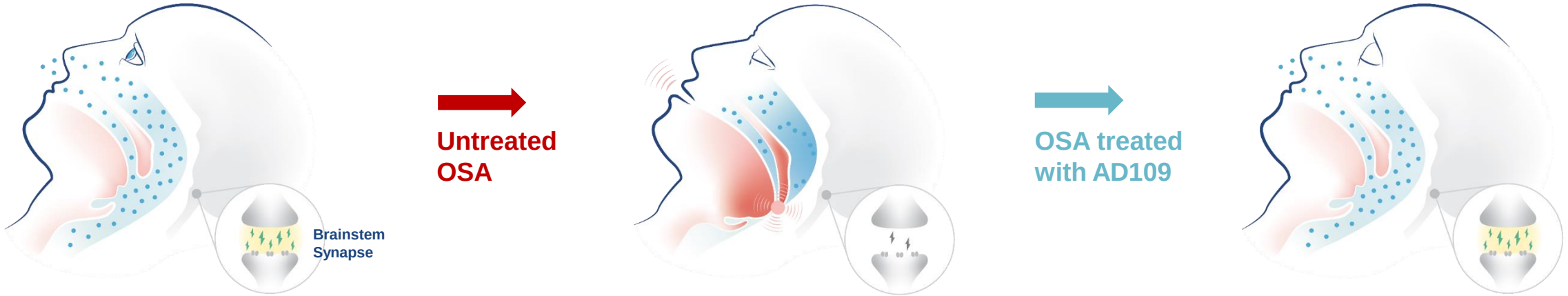




Strollo PJ et al. N Engl J Med 2014;370:139-49

*The recent development of hypoglossal neurostimulation highlights the neurological basis for Obstructive Sleep Apnea*

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




## 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

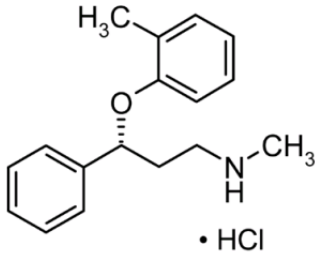
## Airway muscle firing improves, reducing obstructions

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

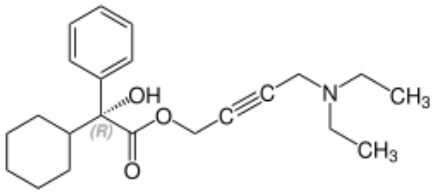
# Our lead program, AD109 combines atomoxetine and a novel antimuscarinic, aroxybutynin

## ATOMOXETINE




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

## AROXYBUTYNIN




**Anti-muscarinic NCE**, active primarily in REM sleep


*Novel AD109 co-formulation of atomoxetine + aroxybutynin*

# Lead program AD109 has shown consistent efficacy on obstruction and oxygen levels in prior Ph2 trials

- Three prior Phase 2 trials of atomoxetine 75mg/aroxybutynin 2.5mg ranging from 1 night to 28 nights
- Rapid onset of action with ~50% improvement in AHI/HB after one night
- Persistent duration of response with no decrement at 28 nights
- Response across the spectrum of OSA, AHI 10-45

| PROTOCOL | SAMPLE SIZE | DOSING DURATION | SIGNIFICANCE VS PLACEBO |
|---|---|---|---|
| APC-003 | n=60 crossover | 1 night | p=0.001 |
| APC-003 OLE | n=37 open label extension | 30 nights | p=0.03 |
| APC-004 | n=31 crossover | 1 night | p<0.0001 |

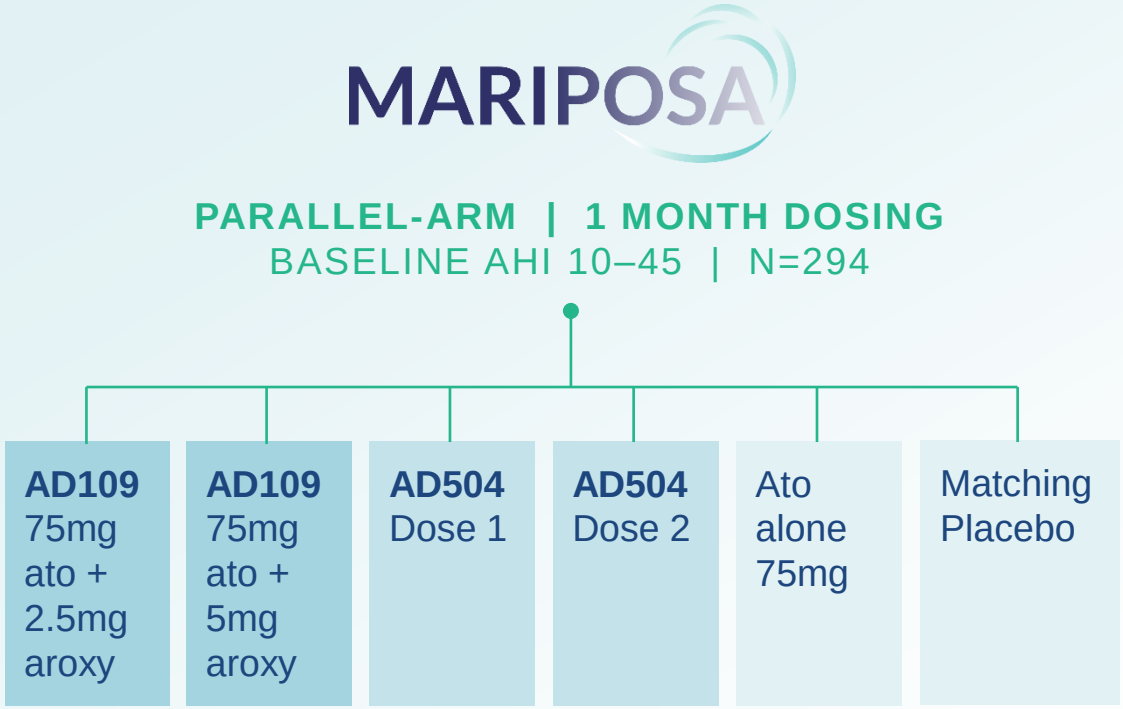
APC-003 results from post-hoc analysis of n=45/60 subgroup with baseline AHI4%<45

# MARIPOSA: A Phase 3-enabling study for AD109

## Study designed to answer key questions and FDA suggestions from Type C meeting

- Additional dose-finding for AD109
- Evaluation of multiple subjective endpoints for P3 incl. PROMIS (key secondary endpoint in this study)
- Atomoxetine and placebo, as control arms
- Also advances AD504 combination

## Primary endpoint: Change in AHI over 1 month



# MARIPOSA trial: Overall outcome & takeaways

ONE

## Robustly positive objective and subjective efficacy for AD109

- Primary Endpoint met: Improvement of airway obstruction
- Key Secondary Endpoints met: Improvement of OSA symptoms
- Key sleep endpoints strongly support mechanism of clinical benefit

TWO

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

- Atomoxetine alone has negative effects on sleep, generally intolerable
- Aroxybutynin *required* for improved OSA symptoms, stable sleep

THREE

## AD109 generally safe and well tolerated

- No SAEs, deaths, or unexpected AEs in topline data

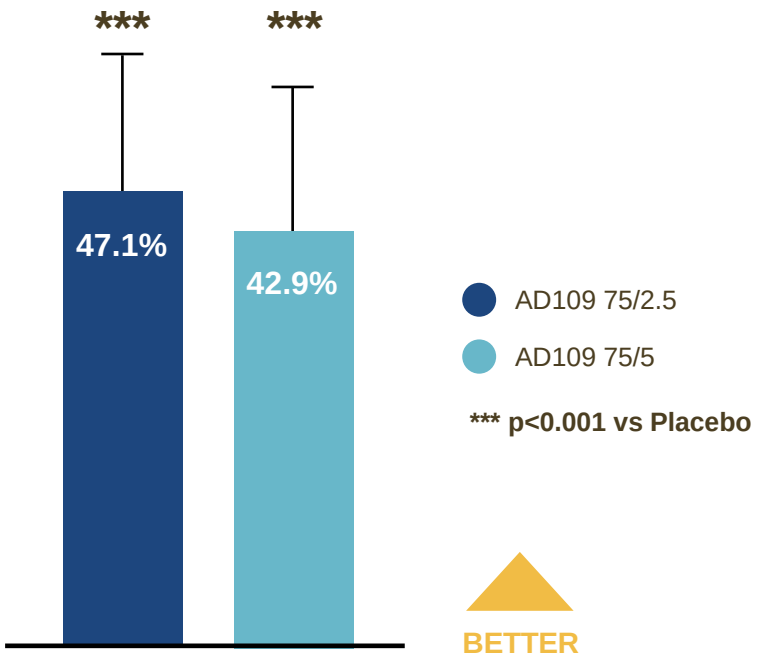
FOUR

## Informative dose-response and exploratory program data

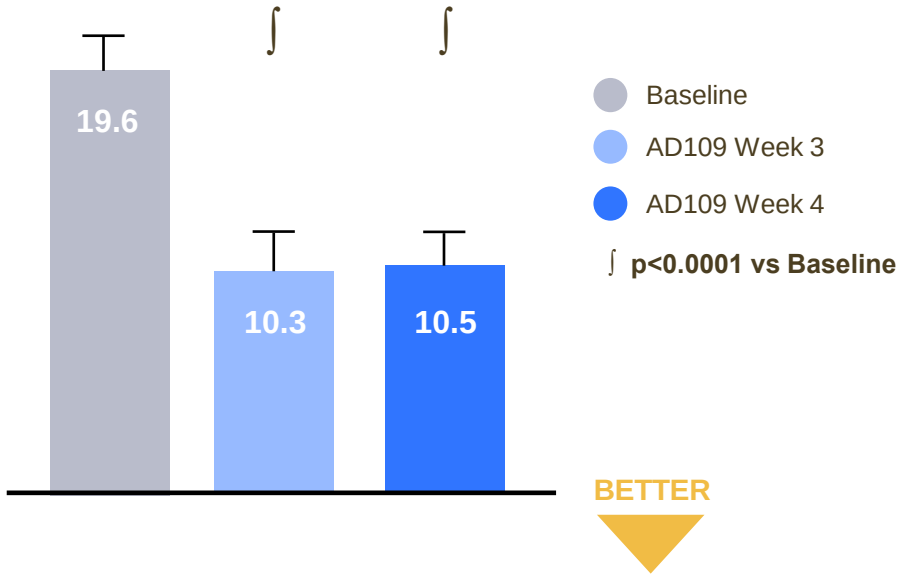
- AD109: Supports continued Ph3 development of 75mg/2.5mg, *standard dose in prior trials*
- AD504: Second program with promising results

# 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*

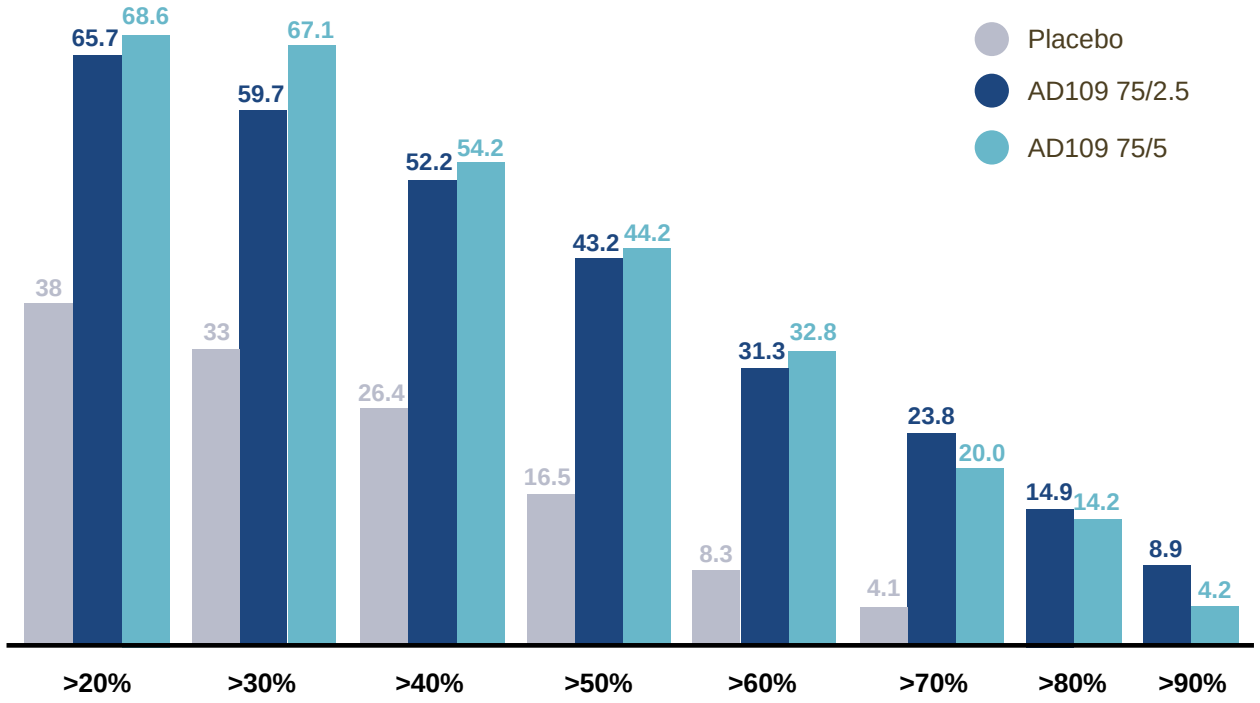
*Stable efficacy over 1 month: reassuring for success over longer 3 month Ph3 duration*

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 (%)

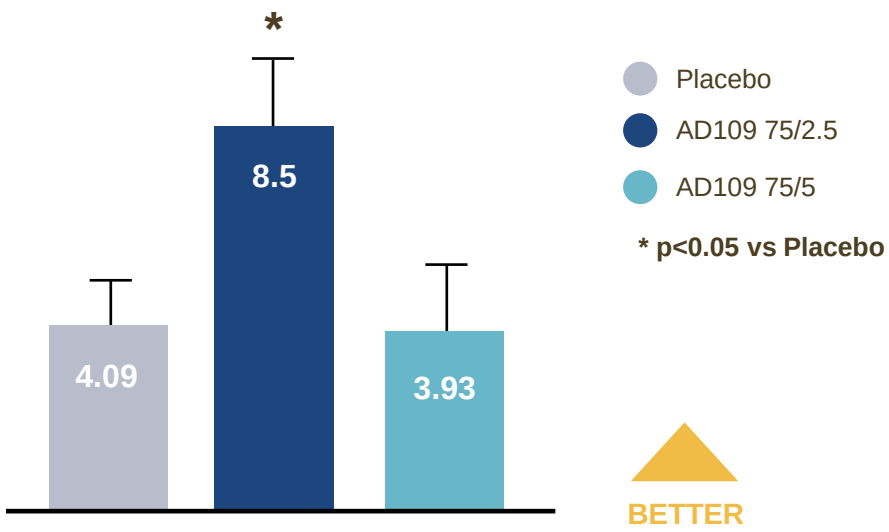



## AHI4 Response by Clinical Severity for the AD109 75/2.5 dose

| CLINICAL CLASSIFICATION | PATIENTS WHO ACHIEVED AHI<10 ON TREATMENT; NO FURTHER Rx MAY BE NEEDED IN CLINCIAL SETTING |
|---|---|
| **Mild OSA**<br>Baseline AHI <15 | 69% |
| **Moderate OSA**<br>Baseline 15≤AHI<30 | 44% |
| **Severe OSA**<br>Baseline AHI ≥30 | 7% |
| **All Patients** | 41% |

# 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 safety and tolerability in MARIPOSA

## COMMON ADVERSE EVENTS % (≥3 PATIENTS)

| *n* | 75/5 [*41*] | 75/2.5 [*42*] | 75ato [*63*] | Pbo [*63*] |
|---|---|---|---|---|
| dry mouth | 59 | 24 | 27 | 5 |
| urinary impairment (any) | 22 | 7 | 22 | 0 |
| insomnia (any) | 22 | 26 | 37 | 3 |
| constipation | 12 | 0 | 3 | 3 |
| nausea | 10 | 12 | 6 | 3 |
| decreased appetite | 10 | 5 | 8 | 2 |
| feeling jittery | 7 | 5 | 3 | 2 |
| somnolence | 7 | 2 | 0 | 2 |
| *Discontinuations from AEs (%)* | *12* | *12* | *19* | *2* |

*All study AEs were mild or moderate, except for two severe AEs experienced by patients taking 75mg atomoxetine alone – "nausea" and "migraine"*

*No Serious Adverse Events (SAEs); no new or unexpected AEs*

*Lower dose AD109 associated with fewer AEs than high dose, or atomoxetine alone*

*AD109 lower dose well tolerated by most patients*

# MARIPOSA sets the stage for an AD109 Phase 3

## Statistically significant and clinically meaningful efficacy at one month, supporting success in Phase 3

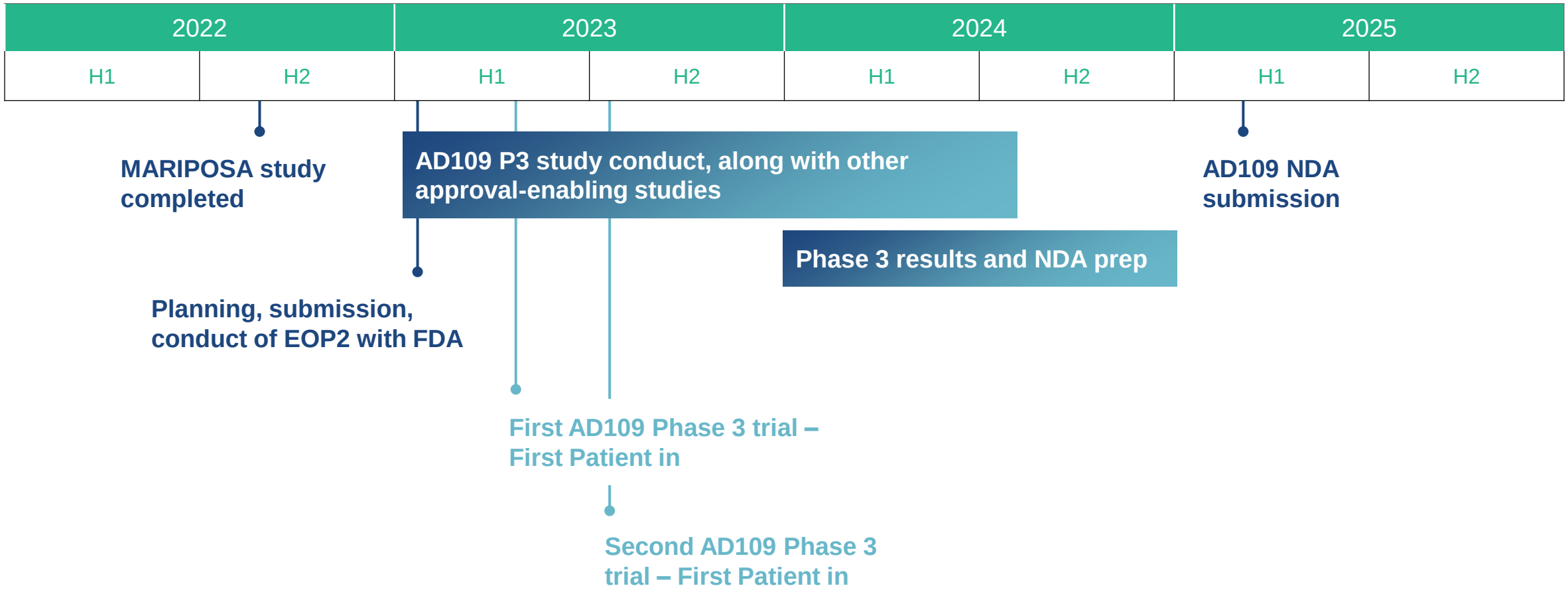
- MARIPOSA incorporated extensive feedback from FDA meetings regarding dose finding and symptom endpoints

## AD109 dose of 75/2.5 is the appropriate dose to proceed to Phase 3

- Best efficacy on OSA symptoms
- Fewer AEs

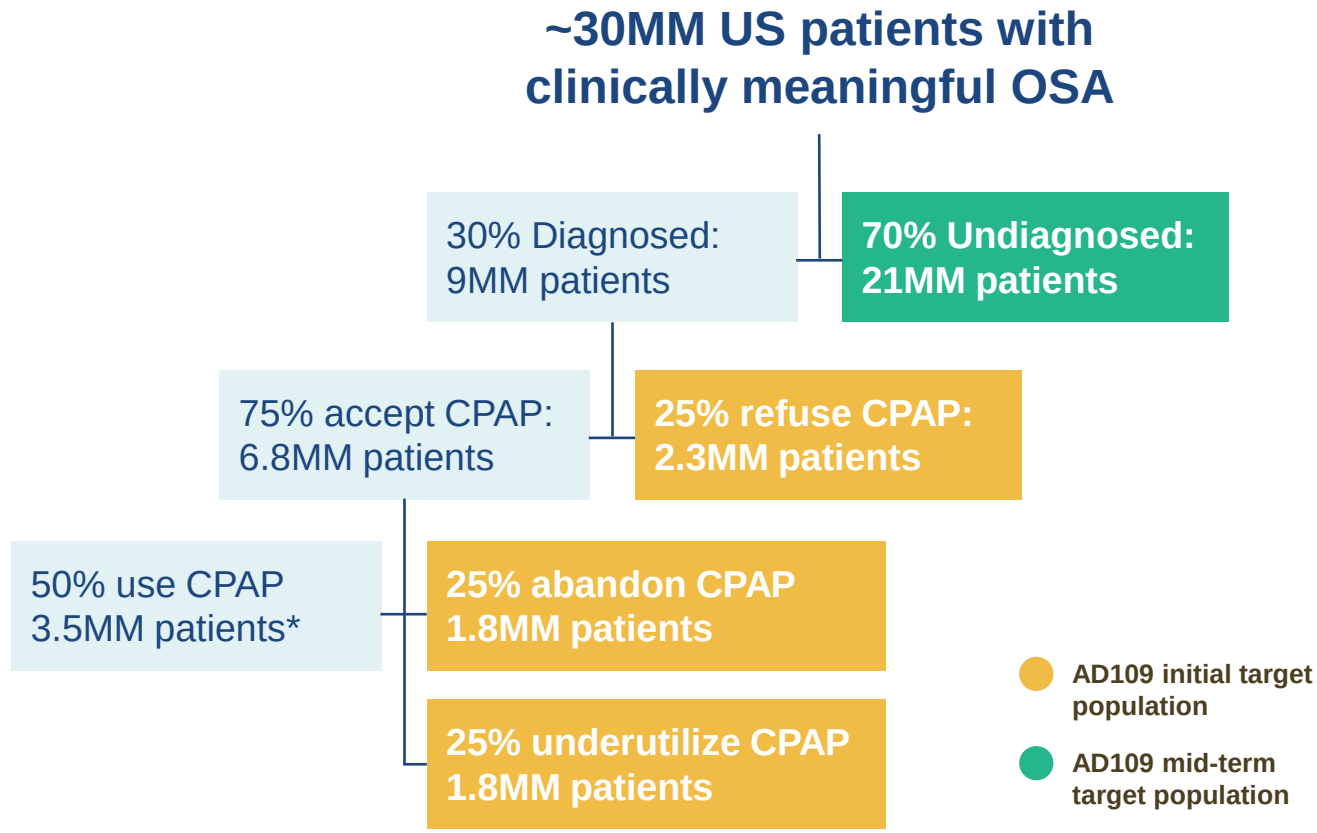
## Supports choice of Phase 3 symptom endpoints

# AD109 path to NDA filing



# 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

# Apnimed has a strong financing history backed by experienced investors

## Completed Series C
*April 2022*

**$62.5mm round**
Led by Sectoral Asset Management.

Also participating: Alpha Wave Ventures, NexPoint, other new investors, and all existing investors (Morningside Ventures, Seligman Investments, and Tao Capital Partners)

## Overall Equity Raised

**$127.5mm raised**
Since inception | June 2018

# 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 will initiate early 2023 with likely NDA filing in late 2024/early 2025**

**Experienced management team and investor syndicate**

Apnimed

THANK YOU