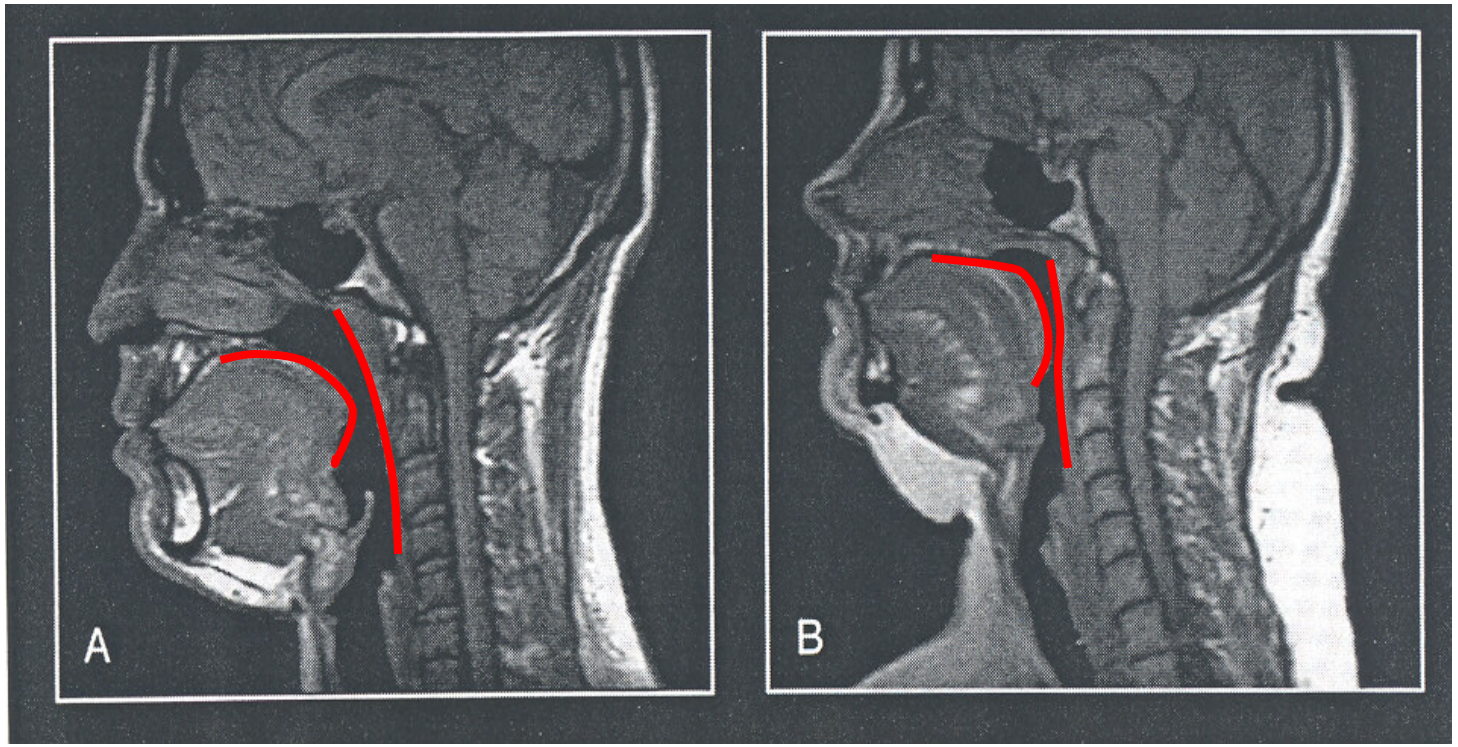
Apnimed

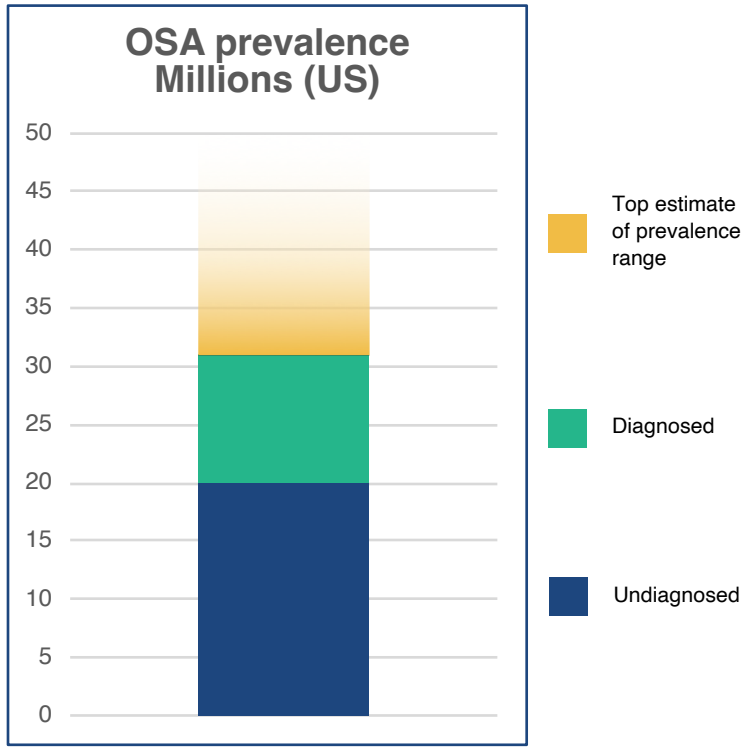
DRUG THERAPY FOR
OBSTRUCTIVE SLEEP APNEA

Jefferies Healthcare Conference I 10 June 2022

Obstructive Sleep Apnea (OSA) is a major clinical disorder (>35M in the US) with huge unmet need



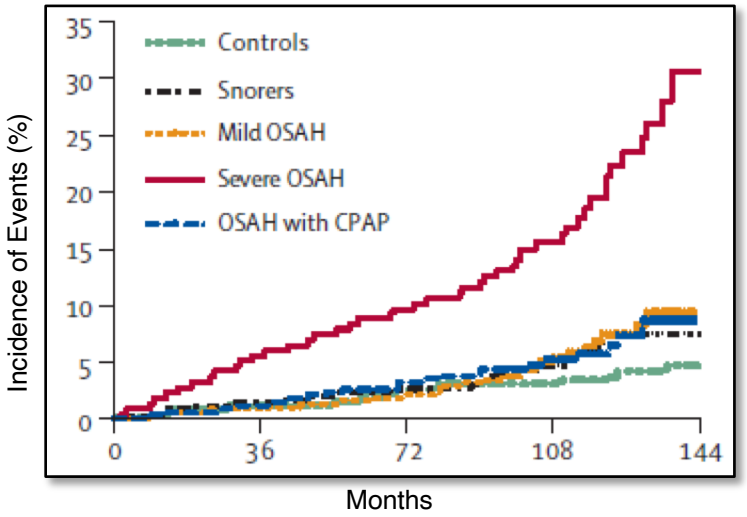
Richard Schwab, Clinics in Chest Medicine, 1998



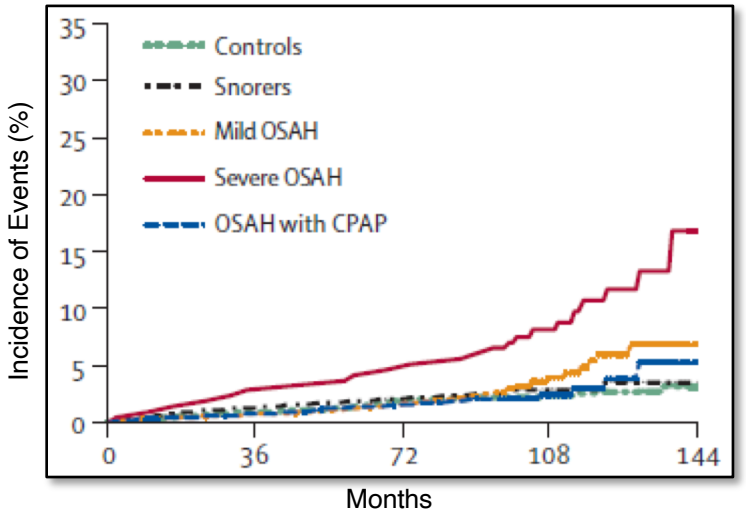
National Healthy Sleep Awareness Project, Young et al., 2009, and Frost and Sullivan, AASM, 2016, Benjafield AV et al 2019

OSA carries significant risk for cardiovascular events

Cumulative incidence of non-fatal CVS events (%)



Cumulative incidence of fatal CVS events (%)



Potential mechanisms for OSA and CVS events

- Oxidative stress
- Sustained sympathetic activation
- Intra-thoracic pressure changes

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

1985

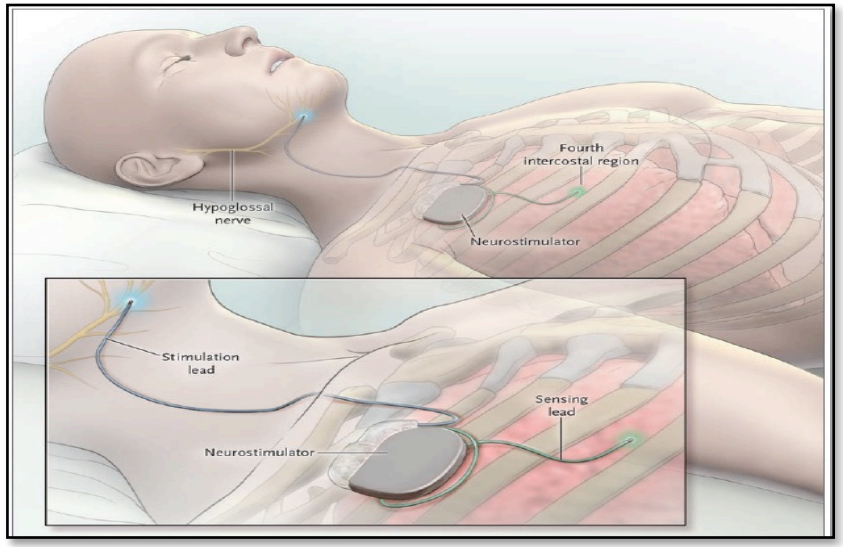
Today

More recent treatments for OSA are poorly tolerated, ineffective, or limited to a subgroup of OSA patients

Oral appliances

Oral appliances, usually Mandibular advancement devices, move the lower jaw forward to enlarge the airway but are often poorly tolerated or ineffective

Implantable neurostimulators

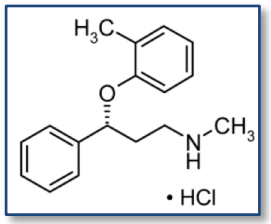


Strollo PJ et al. N Engl J Med 2014;370:139-49

Implanted hypoglossal neurostimulators cause the tongue muscle to contract at night to reduce airway obstruction, but are limited to a small subgroup of OSA patients. A surgical procedure is required at substantial cost

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

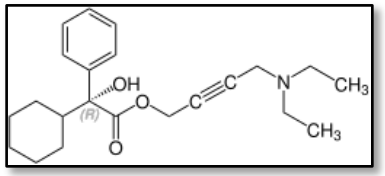
Atomoxetine



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

+

Aroxybutynin



Anti-muscarinic, (R)enantiomer of oxybutynin, NCE, active primarily in REM sleep

Novel AD109 co-formulation of atomoxetine + aroxybutynin

AD109 mechanism of action: Pharmacologic stimulation of the pharyngeal muscles

Reduced muscle firing→ airway obstruction

Reduced phasic contraction of airway muscles leads to obstruction

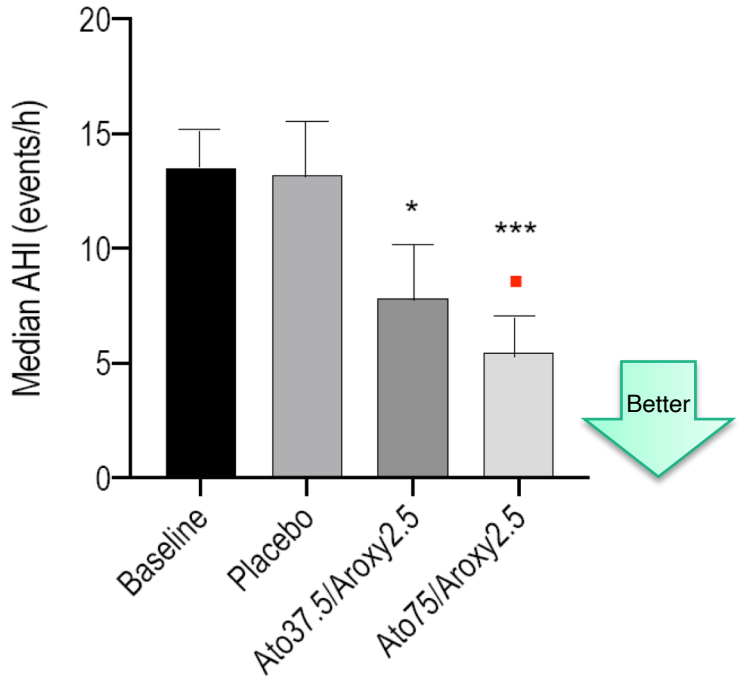
Airway muscle firing improves, limited obstruction

AD109 stimulates increased firing of airway muscles and reduces obstruction

AD109: Positive dose-response in mild/moderate OSA

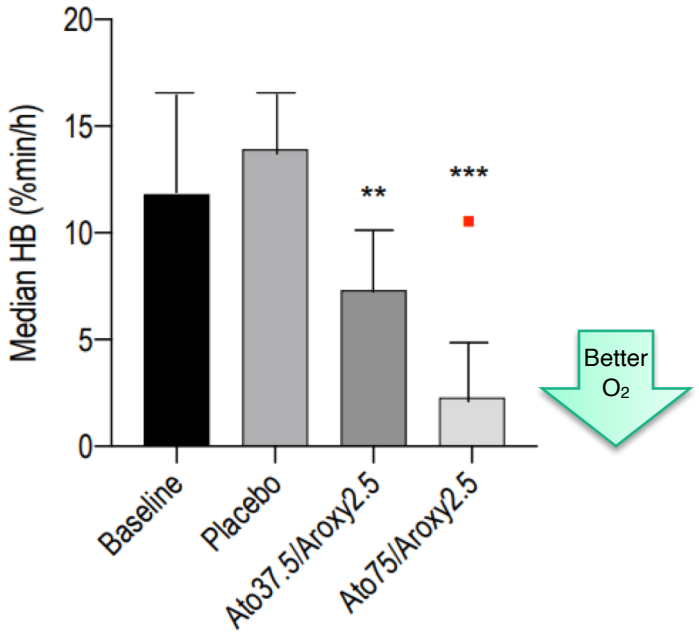
Protocol APC-004: randomized, controlled, 1 night, double-blind, crossover trial with 31 patients with mild-moderate OSA (AHI 5-20, PGI-S ≥1). Study conducted at 3 US sites.

Apnea-Hypopnea Index (AHI)



* p<0.05 vs. placebo
*** p<0.001 vs. placebo
p<0.05 vs. Ato37.5/Aroxy2.5

Hypoxic Burden (HB)

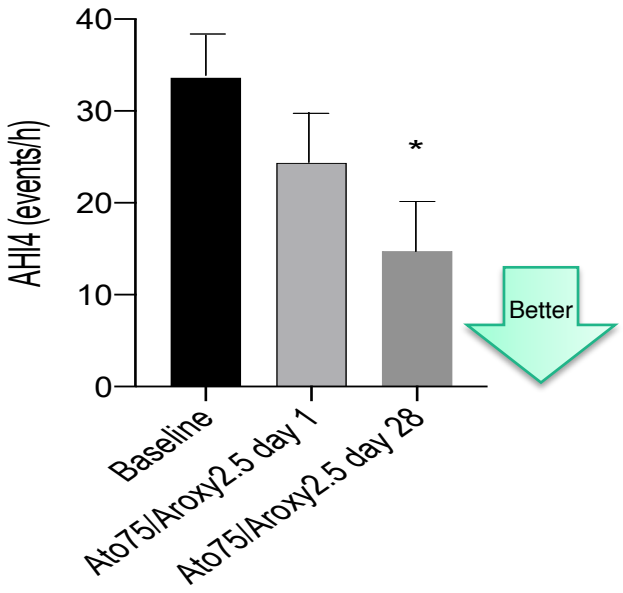


P-values for HB refer to statistical model LOG10(HB4+1), HB and AHI data shown as medians and their SE.
HB: Hypoxic Burden, a quantitative measure of sleep apnea specific overnight oxygen desaturation.

AD109: Durable objective efficacy and symptom improvement over 4 weeks in mild to severe OSA

Apnea-Hypopnea Index

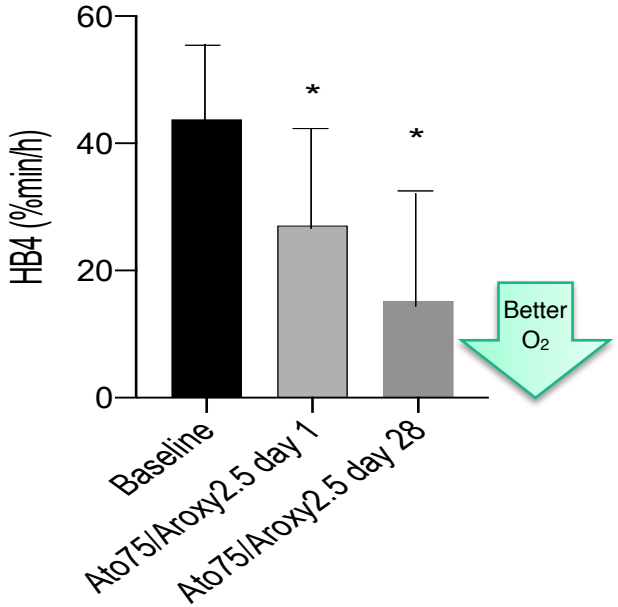
Day 1: APC-003
Day 28: APC-003-OLE



**p<0.05 vs. baseline. AHI and HB data shown are medians and SE of medians*

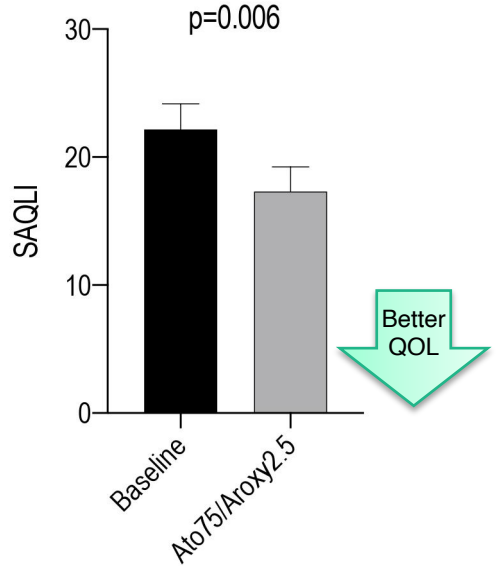
Hypoxic Burden

Day 1: APC-003
Day 28: APC-003-OLE



HB: Hypoxic Burden, a quantitative measure of sleep apnea specific overnight oxygen desaturation

OSA-specific Quality of Life



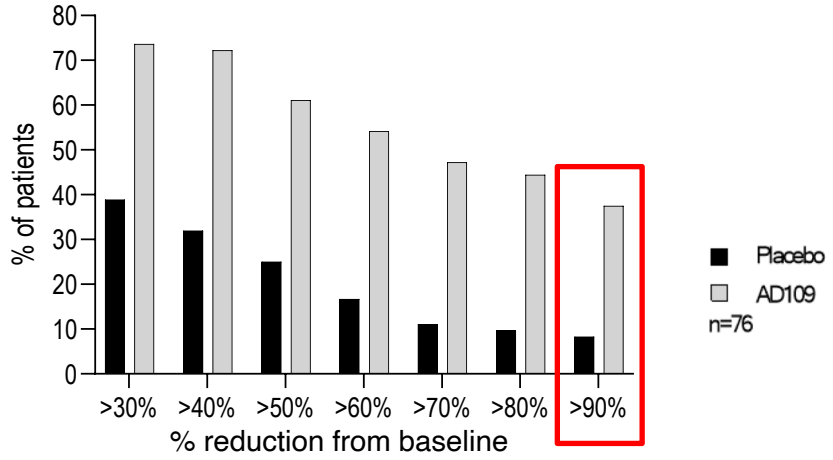
Short SAQLI": a 14-item scale of quality of life in OSA. Clinically meaningful 4-point improvement in major symptoms, for example, snoring, fatigue, daytime sleepiness

Protocol APC-003-OLE: 4-week, open-label extension study of patients from protocol APC-003 with 37 patients with mild-severe OSA (AHI 10-45 or > 45 with airway collapsibility conditions met). Study conducted at 7 US sites.

Responder analysis shows majority of patients have substantial response, large proportion near “cure”

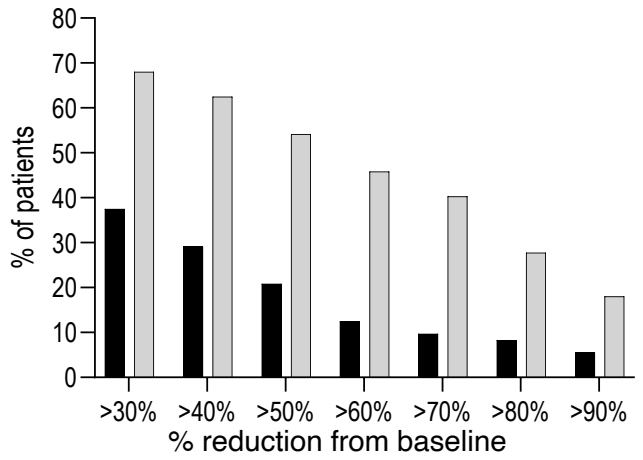
HB% responders in patients with baseline AHI<45

Patients from studies APC-003 and APC-004



AHI % responders in patients with baseline AHI<45

Patients from studies APC-003 and APC-004



Analysis of response rates indicates that the substantial majority of patients had major reductions in HB and AHI with AD109, a clinically significant improvement, ~40% of patients achieving near complete resolution

Protocol APC-003: 1 night, double-blind, crossover factorial trial with no low-dose run-in, 62 patients with mild-severe OSA (AHI 10-45 or > 45 with airway collapsibility conditions met).
Protocol APC-004: randomized, controlled, 1 night, double-blind, crossover trial with 31 patients with mild-moderate OSA (median AHI 13.5 events/h).

AD109: Consistent efficacy across trials

Drug	Protocol	Dosing Duration And Sample Size	% reduction in median AHI[1] / HB	Significance vs. Placebo
AD036 (ato/oxy)	APN-002	10 nights; n=140 parallel-arm	61% / 54%[2]	p=0.009
AD036 (ato/oxy)	APN-006	1 night; n=62 crossover	56% / 52%	p<0.0001
AD109 (ato/aroxy)	APC-003	1 night; n=60 crossover	70% / 78%[3]	p=0.001
AD109 (ato/aroxy)	APC-003 OLE	30 nights; n=37 open label extension	56% / 65%	p=0.03
AD109 (ato/aroxy)	APC-004	1 night; n=31 crossover	59% / 80%	p<0.0001

- >300 patients treated
- Highly clinically meaningful effect
- Similar to CPAP[4] and neurostimulation.[5]

1. AHI4% (Medicare definition used). Median reductions shown are relative to either placebo or baseline, as appropriate per protocol. Results reported for full dose – 75/5 or 75/2.5 for AD036 and AD109, respectively.
2. APN-002 results from post-hoc analysis of n=102/140 subgroup with baseline AHI4%<55.
3. APC-003 results from post-hoc analysis of n=45/60 subgroup with baseline AHI4%<45
4. Boyd SB et al. SLEEP, Vol. 39, No. 11, 2016
5. Strollo PJ et al. N Engl J Med 2014;370:139-49.

AD109: Well tolerated over multiple studies

- AE's consistent with approved labeling of atomoxetine and oxybutynin

Protocol	Category n (%)	Ato 75/Aroxy 2.5 (N = 56)	Ato 75 (N = 54)	Aroxy 2.5 (N = 54)	Placebo (N = 57)
APC-003 single night crossover	GERD	2 (3.6)	2 (3.7)	0	0

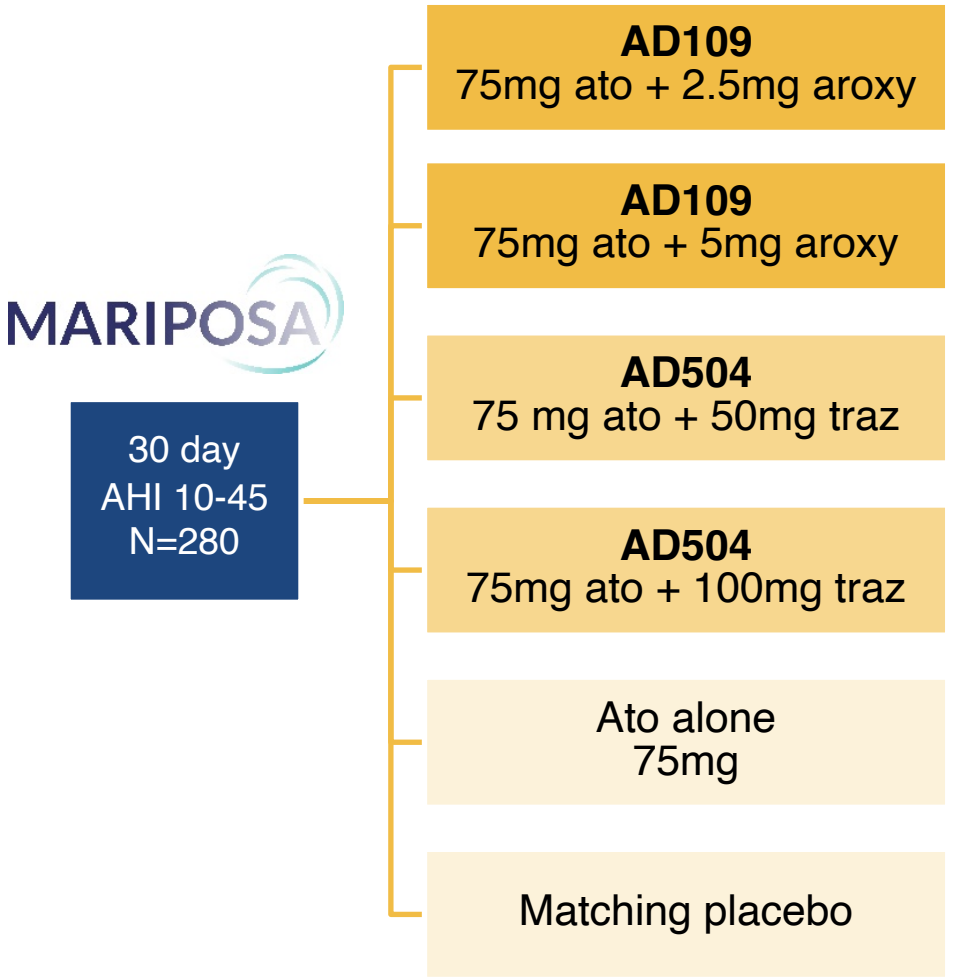
Protocol	Category n (%)	Ato 75/Aroxy 2.5 (N = 30)	Ato 37.5/Aroxy 2.5 (N = 28)	Placebo (N = 29)
APC-004 single night crossover	Dry Mouth Decreased appetite	2 (7) 2 (7)	2 (7) 0	1 (3) 0

- No change in blood pressure
- Minimal change in pulse (2 bpm increase)
  - Similar to stimulants approved for symptom of excessive daytime sleepiness (e.g. Sunosi®)
- No next-day functional impairment
  - Testing (DSST) showed improvement for higher dose arm

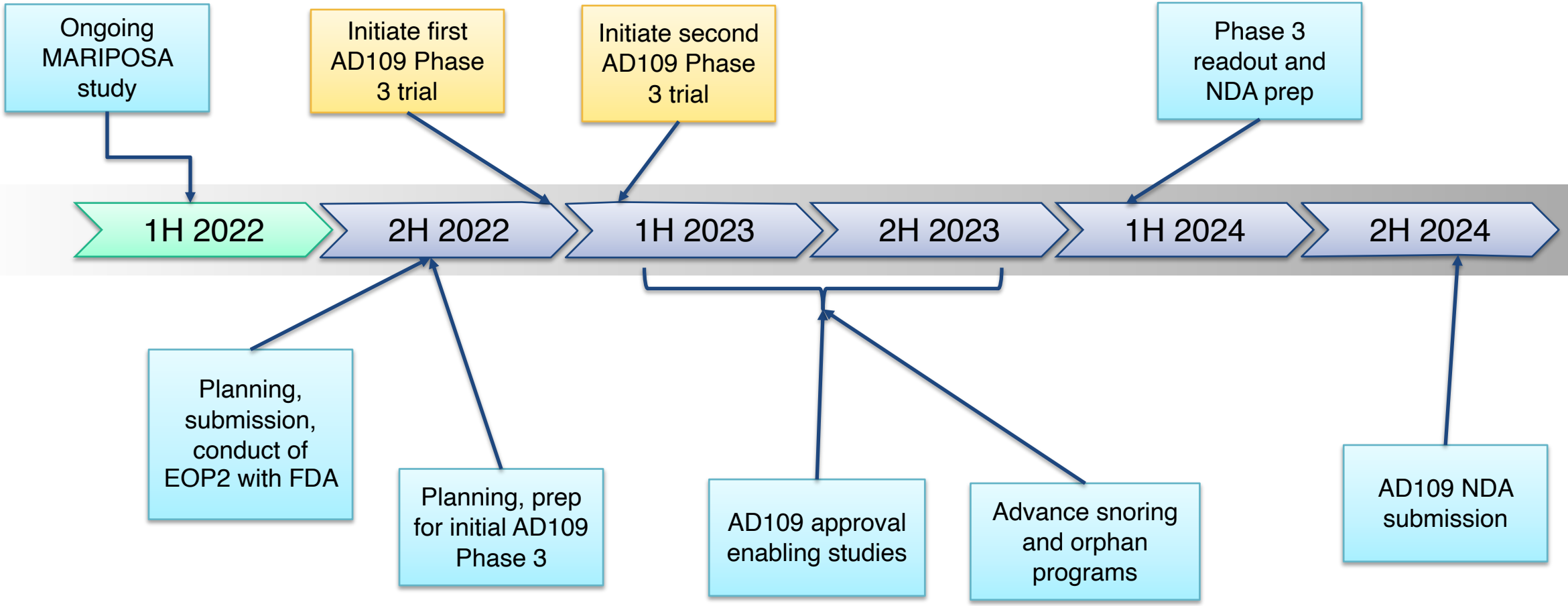
AEs shown that occurred in 2 or more patients of drug arm

MARIPOSA: a Phase 3-enabling study for AD109

- FDA-required additional dose-finding for AD109
  - Also advances atomoxetine & trazodone combination (AD504)
- Atomoxetine alone, placebo, as control arms
- Evaluation of multiple subjective endpoints for Phase 3, per FDA
- First dose Dec 2021, recruiting as planned, topline expected 3Q22

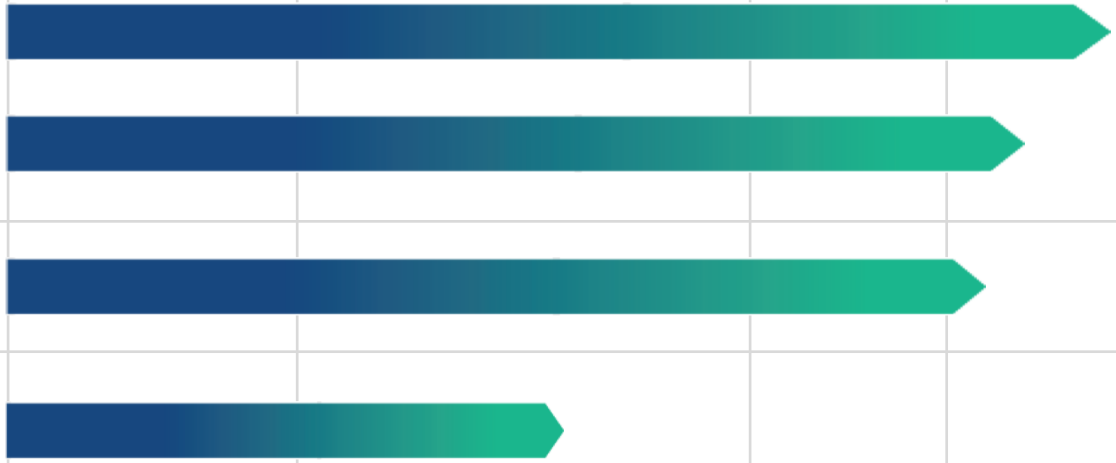


Path to NDA submission and approval



Apnimed development pipeline

Program	Indication/ Formulation	Pre-clinical	Exploratory Clinical	P1	P2	P3
AD109 (ato+aroxybutynin)	OSA					
	Snoring					
AD504 (ato+trazodone)	OSA w/ disturbed sleep Novel formulation					
Other programs	Monotherapy or combination alternatives for OSA or snoring					



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, and others

Existing investors: Morningside Ventures, Seligman Investments, and Tao Capital Partners

Overall Equity Raised

$127.5mm raised since inception (June 2018)

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

- OSA is a serious 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 begin later this year with likely NDA filing in 2024
- Experienced management team and investor syndicate

Thank You