Demographic and Baseline Disease Characteristics of SynAIRgy: A Phase 3 Trial of Aroxybutynin and Atomoxetine (AD109) in Obstructive Sleep Apnea

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SynAIRgy

INTRODUCTION

- OSA is characterized by sleep-related neuromuscular dysfunction (such as decreased upper airway muscle tone) and predisposing anatomic abnormalities (narrowed upper airway)[1-4]
- No FDA-approved drugs are currently available to address the neuromuscular dysfunction of OSA
- AD109 is a combination of a novel antimuscarinic, aroxybutynin (R-enantiomer of oxybutynin), and the selective norepinephrine reuptake inhibitor, atomoxetine[5]
- In the phase 2b MARIPOSA study where participants received 1 month of AD109, there was[5]:
  - Clinically significant reduction in AHI_4 versus placebo (−7.16 events/hour [47.1% reduction]; 95% CI, −11 to −3.3; P<0.001)
  - Significant reduction in PROMIS-Fatigue score versus placebo (−3.56; 95% CI, −6.77 to −0.35; P<0.05)

METHODS

- SynAIRgy is a multicenter, randomized, double-blinded, placebo-controlled, 6-month, parallel-arm phase 3 study in adults with mild to severe OSA who are intolerant to, or currently refuse, PAP therapy (**Figure 1**)
- Separately, a 1-year phase 3 study, LunAIRo (NCT05811247), is ongoing in 660 participants with mild to severe OSA, with similar enrollment criteria
- Participants completing LunAIRo or SynAIRgy have the option to enter an open label extension study (NCT06566820)

Table 1. Key inclusion and exclusion criteria

Inclusion

OSA history and measures
- PSG criteria:
  1. AHI_4[a] >5
  2. ≤25% central or mixed apneas (as proportion of total apneas + hypopneas)
  3. PLM arousal index ≤15
- PROMIS-Fatigue Short Form 8a: raw score ≥17 at visit 1
- PAP failure[b] or PAP refusal[c]

Weight

BMI: between 18.5 and 40 kg/m^2 for men, or 18.5 and 42 kg/m^2 for women

Exclusion

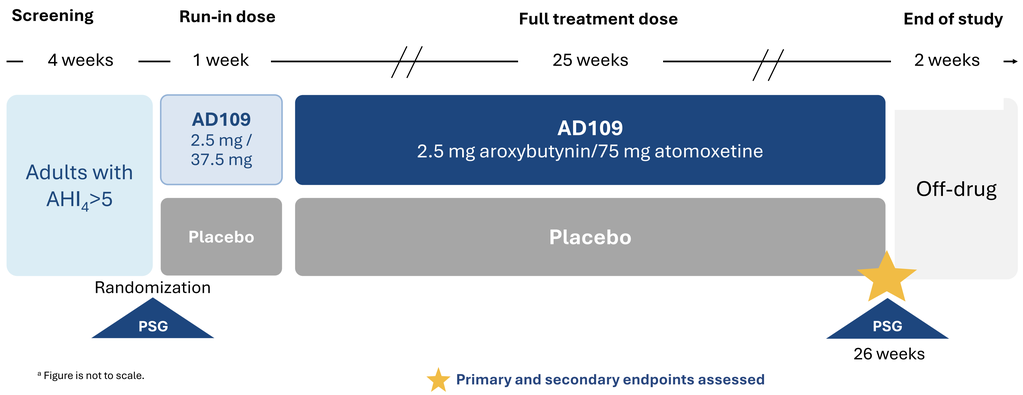
Medical conditions
- Narcolepsy, RLS requiring medication, REM sleep behavior disorder
- Current bothersome symptoms of insomnia
- Clinically significant or medically uncontrolled CVD, or resting HR >100 bpm, untreated or unstable coronary artery disease, HF, cerebrovascular event, or revascularization within 3 months
- Blood pressure >145/90 mmHg
- Women who are pregnant or nursing

[a] Hypopneas are defined as a reduction in airflow ≥30% associated with ≥4% oxygen desaturation.
[b] PAP failure is no PAP use for ≥3 months before randomization, or return/removal of PAP device from home.
[c] PAP refusal is refusal of PAP after prior positive sleep study, or prior refusal of provider-recommended sleep study due to unwillingness to consider PAP.

KEY TAKEAWAYS:

- SynAIRgy has been completed, with 646 participants randomized in a 1:1 ratio to receive either AD109 or placebo
- Participants randomized exhibit baseline AHI_4 across all OSA severities and a wide range of weight classes
- The participants enrolled are representative of the diverse demographic composition of the United States and reflect the symptom profiles of a typical sleep clinic referral OSA population

Figure 1. Study Design[a]



[a] Figure is not to scale.

Table 2. Key objectives and endpoints

Objectives	Endpoints
Primary objective Compare efficacy on airway obstruction of AD109 versus placebo in participants with mild to severe OSA	**Primary endpoint** • Change in AHI_4 at Week 26
Secondary objectives Compare efficacy on OSA symptoms and oxygenation of AD109 versus placebo in participants with mild to severe OSA	**Secondary endpoints** The following are assessed as change from baseline at Weeks 26: • ODI_3 • PROMIS-Fatigue • Hypoxic burden (HB4) • PROMIS-Sleep Impairment • Proportion of participants with ≥50% reduction in AHI_4

DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

Table 3. Demographics of Participants Enrolled

Characteristic	SynAIRgy (N=646)
Age (yrs), mean (SD)	57.1 (11.0)
BMI (kg/m^2), mean (SD)	32.3 (5.0)
BMI, n (%)	
<25	46 (7.1)
25–<30	172 (26.6)
30–<35	225 (34.8)
≥35	203 (31.4)
Sex, n (%)	
Female	317 (49.1)
Male	329 (50.9)
Race, n (%)	
American Indian or Alaskan Native	7 (1.1)
Asian	49 (7.6)
Black or African American	134 (20.7)
Native Hawaiian or Other Pacific Islander	4 (0.6)
Other	5 (0.8)
White	443 (68.6)
Not Reported	2 (0.3)
Unknown	2 (0.3)
Ethnicity, n (%)	
Hispanic or Latino	138 (21.4)
Not Hispanic or Latino	505 (78.2)
Not Reported	2 (0.3)
Unknown	1 (0.2)

Table 4. Baseline Disease Characteristics of Participants Enrolled

Characteristic	SynAIRgy (N=646)
AHI_4, mean (SD)	22 (11)
AHI_4 severity, n (%)	
Mild, AHI_4 5 – <15	222 (34.4)
Moderate, AHI_4 15 – <30	274 (42.4)
Severe, AHI_4 ≥30	150 (23.2)
ODI_3, mean (SD)	29.0 (13.0)
PROMIS-Fatigue T-score, mean (SD)	59.1 (7.0)
PROMIS-SI T-score, mean (SD)	58.5 (7.5)
PGI-S for Fatigue, mean (SD)	3.0 (0.8)
ESS, mean (SD)	10.1 (4.7)
HB4, mean (SD)	43 (40)

ABBREVIATIONS

AHI, apnea-hypopnea index; AHI_{3a}, AHI with a ≥3% decrease in oxyhemoglobin saturation or an event-related arousal; AHI_4, AHI with a ≥4% decrease in oxyhemoglobin saturation; BMI, body mass index; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale; HB4, hypoxic burden with 4% desaturation criterion; HF, heart failure; HR, heart rate; ODI, oxygen desaturation index; ODI_3, 3% oxygen desaturation index; OSA, obstructive sleep apnea; PAP, positive airway pressure; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; PLM, periodic limb movement; PROMIS-Fatigue, Patient-Reported Outcomes Measurement Information System – Fatigue; PROMIS-SI, Patient-Reported Outcomes Measurement Information System – Sleep Impairment; PSG, polysomnography; REM, rapid eye movement; RLS, restless legs syndrome; SD, standard deviation.

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DISCLOSURES

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Scan for SynAIRgy trial update.