From sleepless nights to restored days: How AD109 is giving obstructive sleep apnea patients their lives back

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BRIEF INTRODUCTION

Breathing is a vital physiological process that sustains life by enabling continuous gas exchange. Disruptions during sleep—such as those caused by obstructive sleep apnea (OSA), a common sleep disorder affecting over 1 billion people worldwide—pose serious health risks. Recently, the field of sleep medicine has achieved a landmark milestone. Apnimed has announced that its potential "first-in-class" oral candidate drug AD109 has demonstrated significant positive results in the pivotal Phase 3 clinical trial SynAIRgy for the treatment of OSA. For decades, many patients have relied on continuous positive airway pressure (CPAP) devices during sleep to maintain ventilation, but these treatments have limited efficacy, and most patients struggle to adapt to the discomfort of wearing the devices. As the world's first oral drug to directly act on airway muscles, AD109 has fundamentally transformed the therapeutic logic for OSA. This model of "active regulation" rather than "passive support" shifts OSA treatment from pure device dependence to pharmacological intervention, offering patients a more natural and comfortable option (Figures 1A-C).

DEFINITION AND CURRENT CLINICAL TREATMENT MODALITIES OF OSA

OSA is primarily caused by the collapse of soft tissues in the upper airway during sleep, leading to recurrent apneas and hypopneas (≥30% reduction in airflow with oxygen desaturation).[1] Beyond a sleep disorder, OSA is a chronic multisystem disease, particularly associated with increased incidences of cardiovascular and metabolic diseases, daytime somnolence, neurocognitive impairment, and reduced quality of life.[2] Consequently, its disease burden on healthcare systems in real-world settings is incalculable. Currently, CPAP remains the first-line treatment for OSA in clinical practice, but patients often discontinue use due to discomfort from mask pressure, nasal dryness, and other issues, resulting in poor long-term adherence. Additionally, the devices require regular maintenance and are inconvenient to carry.[3] Alternative treatment options such as oral appliances, upper airway surgery, and hypoglossal nerve stimulation depend on individual patient characteristics, making it impossible to form a universally applicable standard treatment protocol.[4] In summary, the therapeutic objectives for OSA are to eliminate sleep-related apneic events, correct sleep-time hypoxemia, enhance sleep quality and quality of life, and reduce the incidence of OSA-related comorbidities and mortality.

ABOUT AD109 AND THE SYNAIRGY STUDY

AD109 is not a completely novel therapy but belongs to the category of "repurposing old drugs." This medication is a combination of the selective norepinephrine reuptake inhibitor atomoxetine and the antimuscarinic drug aroxybutynin. It addresses the fundamental problem of OSA by enhancing upper airway muscle tone during sleep (Figure 1C).

The Phase II MARIPOSA trial utilized a multi-dose parallel design to determine the optimal therapeutic window for AD109 while revealing that it does not exhibit serious side effects.[5] The success of MARIPOSA prompted the expansion of enrollment in the Phase III trials. SynAIRgy, the largest Phase III clinical trial evaluating a pharmacotherapy for OSA, was a randomized, double-blind, placebo-controlled, parallel-arm study of AD109—a fixed-dose combination of aroxybutynin 2.5 mg/atomoxetine 75 mg—in participants with OSA who are intolerant to or actively refuse CPAP therapy. Conducted across 73 centers in the US and Canada, the trial enrolled 646 adult participants, who were randomized in a 1:1 ratio to receive either AD109 or placebo. All participants were instructed to administer their assigned

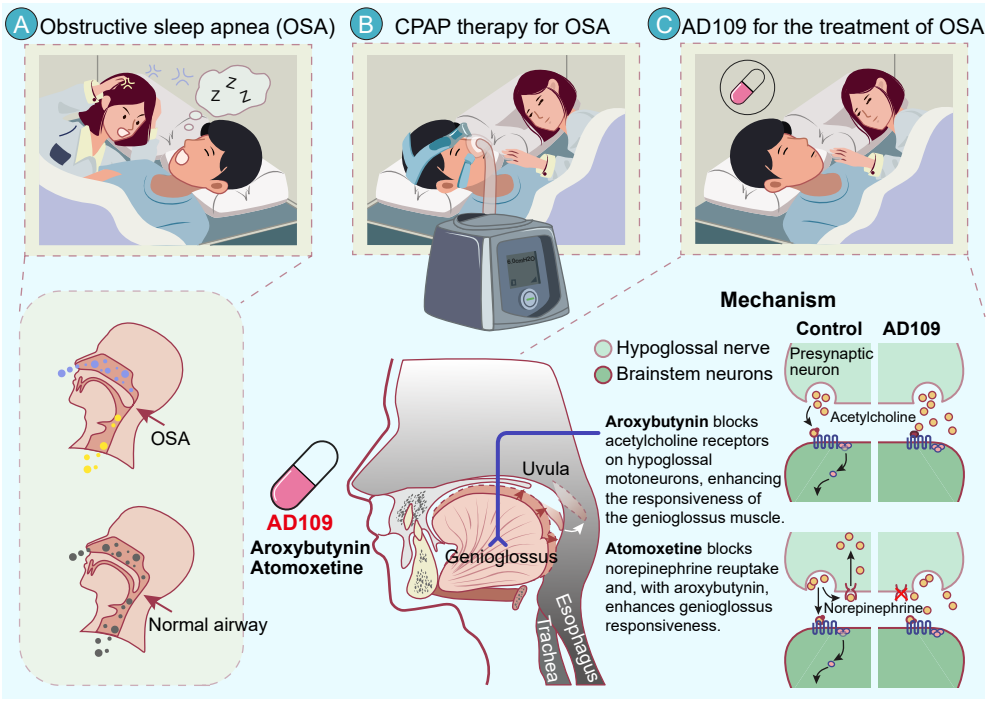

Figure 1. Mechanism of AD109 in the treatment of OSA (A) OSA is characterized by recurrent upper airway obstruction during sleep, resulting in loud, irregular snoring and intermittent breathing pauses that can significantly impair both the patient's and bed partner's sleep quality. (B) CPAP therapy maintains airway patency via a mask but is often limited by inconvenience, discomfort, and poor adherence. (C) AD109 exerts its regulatory effects on the brainstem-hypoglossal nerve pathway through a dual-component mechanism: aroxybutynin blocks muscarinic receptors (M2/M3) on hypoglossal motor neurons, relieving acetylcholine-mediated inhibition of these neurons. Concurrently, atomoxetine inhibits the norepinephrine transporter (NET) on presynaptic membranes, increasing norepinephrine concentration in synaptic clefts to activate α1-adrenergic receptors. This synergistic action enhances the excitability of hypoglossal nerves, thereby promoting the active contraction of upper airway muscles such as the genioglossus. Specifically, aroxybutynin improves the responsiveness of genioglossus muscles to hypoxic stimuli, while atomoxetine enhances upper airway smooth muscle tone, collectively maintaining airway patency during sleep.

treatment once daily before bedtime. Although complete data have not yet been published, publicly available information indicates that after 26 weeks of treatment, the average apnea hypopnea index (AHI) in the experimental group decreased by 55.6% from baseline, with significant improvements in oxygen saturation and disease severity. Among the trial participants, 51.2% experienced at least a one-level reduction in OSA severity, and 22.3% achieved a complete control standard with an AHI of <5 events per hour.

These results have heightened anticipation for Lunairo, the parallel trial to SynAIRgy, which is expected to be announced in the third quarter of 2025 and will further validate the long-term utility of AD-109. Even more exciting is Apnimed's plan to submit a New Drug Application (NDA) to the U.S. FDA in early 2026. The FDA has granted it "Fast Track" designation to accelerate the approval process.

DIFFERENTIATED COMPETITIVE LANDSCAPE OF CURRENT OSA DRUGS

In the field of OSA treatment, AD109, as the world's first oral drug directly acting on airway muscles, forms a differentiated competitive landscape with other potential drug therapies. Its core advantage lies in directly enhancing airway tone during sleep, covering all weight categories of OSA patients without relying on weight loss, and demonstrating significant efficacy, particularly in M-type (muscle hypo-responsiveness) OSA. This mechanism of direct airway regulation gives it an irreplaceable position in non-obese or mild OSA patients, while the convenience of oral administration (once daily before bedtime) further improves long-term compliance, especially for patient's intolerant of CPAP ventilators.

In contrast, GLP-1 drugs (such as Tirzepatide, Mazdutide, HRS9531) indirectly improve airway fat accumulation by activating GLP-1/GIP receptors but are only suitable for obese patients. For example, Lilly's Tirzepatide was approved by the FDA in December 2024 for treating adult patients with moderate-to-severe OSA complicated by obesity, making it the first globally approved drug for direct OSA treatment. However, it is only applicable to individuals with a BMI ≥30 kg/m² and an AHI ≥15 events/hour, requires weekly injections, and may cause gastrointestinal side effects. As a domestic Chinese-developed GCG/GLP-1 dual receptor agonist, Mazdutide showed outstanding weight loss efficacy in phase III trials (13.38% weight reduction in the 6 mg group) and can reduce liver fat content, but its OSA indication remains in the phase III planning stage with unvalidated direct efficacy (GLORY-OSA). Similarly, while Hengrui's HRS9531 has demonstrated significant weight loss effects in obese patients (22.8% weight reduction in the 8 mg group), clinical trials for OSA with obesity have just been approved, and data are pending verification.

For central modulators like BIOS-0618, it improves daytime somnolence in OSA patients by regulating the central nervous system, but its specific mechanism remains unclear, and it only targets daytime symptoms without addressing nighttime respiratory events.

As the first oral drug directly acting on airway muscles, AD109 fills the treatment gap for non-obese OSA patients, while GLP-1 drugs dominate the obese OSA field through weight loss and metabolic regulation. In the future, precision stratified treatment and combination therapy may become the mainstream direction for OSA management, while clinical progress of new central modulators (such as BIOS-0618) should be monitored. With the launch or advancement of drugs like AD109 and Mazdutide, OSA treatment will shift from single symptomatic management to mechanism-driven comprehensive intervention.

LIMITATIONS OF AD109

Notwithstanding the unprecedented potential of AD109 in treating OSA, its potential drawbacks warrant attention. First, the ongoing Phase III SynAIRgy trial has only covered a 26-week treatment period, lacking long-term data on sustained efficacy (e.g., over 5 years) and its impact on reducing cardiovascular events or mortality. Patient enrollment should further consider special populations such as children, pregnant women, the elderly, and those with severe comorbidities, as well as OSA patients with different phenotypes. This will enable us to obtain sufficient clinical evidence to rationally observe the side effects of AD109 and avoid risks of drug interactions. For example, atomoxetine is a major metabolic substrate of CYP2D6. Co-administration with strong CYP2D6 inhibitors (such as fluoxetine and paroxetine) can significantly increase its plasma concentration, leading to an increased risk of side effects such as palpitations, elevated blood pressure, and anxiety.

In terms of patient compliance and practical application, daily bedtime administration may lead to missed doses or discontinuation due to minor side effects (anticholinergic side effects such as dry mouth), potentially affecting long-term efficacy. Therefore, on the path of practicing precision medicine, AD109 still faces challenges.

CONCLUSION AND FUTURE PERSPECTIVES

AD109, as the first oral therapy targeting upper airway muscles, presents a convenient and transformative alternative to CPAP, particularly for non-obese patients or those intolerant to device-based treatments for OSA. Nonetheless, AD109 faces significant challenges, including the ongoing need to robustly demonstrate its long-term safety and efficacy, as well as to effectively position itself against established therapies and competing pharmaceuticals to secure recognition of its clinical value among physicians and patients. As the development of AD109 advances, future research should focus on optimizing treatment protocols and conducting comprehensive pharmacoeconomic evaluations to strengthen the academic foundation supporting its clinical adoption and broader dissemination. Equally important will be investigating its efficacy and safety across diverse patient populations, including special groups such as the elderly, children, and pregnant women, as well as exploring combination regimens with other therapeutic agents.

Looking ahead, AD109 is well-positioned to become a cornerstone in mechanism-driven treatment of OSA; however, its sustained clinical impact will rely on strategic integration into real-world practice. Comparative effectiveness studies against standard treatments like CPAP, oral appliances, and GLP-1 receptor agonists —particularly within phenotypically distinct OSA subgroups —are warranted. Given its pharmacological action in enhancing upper airway muscle tone, AD109 may offer superior benefit in patients with muscle hypo-responsiveness or those without prominent obesity-related airway collapse. In this regard, precision medicine approaches that incorporate polysomnographic data and underlying pathophysiological characteristics could optimize patient selection and improve therapeutic outcomes.

Furthermore, emerging combination strategies —such as co-administration of AD109 with weight-loss agents (e.g., GLP-1 analogs) or central nervous system modulators (e.g., BIOS-0618) —hold promise for delivering more comprehensive, stratified care. These multimodal regimens could more effectively address the multifactorial pathogenesis of OSA by targeting both anatomical and neuromuscular contributors. Concurrently, real-world evidence, digital adherence monitoring, and long-term studies linking AD109 to reductions in cardiovascular risk, cognitive decline, and healthcare utilization will be crucial to inform clinical guidelines and facilitate payer acceptance.

In sum, AD109 represents not only a significant pharmacological innovation but also a potential catalyst for redefining therapeutic standards in sleep medicine. Its success could pave the way for future oral therapies, establish new paradigms in phenotype-guided OSA management, and contribute to a more individualized, accessible, and effective treatment landscape.

REFERENCES

1. Benjafield A.V., Ayas N.T., Eastwood P.R., et al. (2019). Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. *Lancet Respir. Med.* **7**:687–698. DOI:10.1016/S2213-2600(19)30198-5
2. Gleeson M. and McNicholas W.T. (2022). Bidirectional relationships of comorbidity with obstructive sleep apnoea. *Eur. Respir. Rev.* **31**:210256. DOI:10.1183/16000617.0256-2021
3. Toh S.T. (2023). Pharmacotherapy for obstructive sleep apnea: Reality or Pipe Dream. *Sleep Med. Rev.* **70**:101817. DOI:10.1016/j.smrv.2023.101817
4. Martinez-Garcia M.A., Campos-Rodriguez F., Barbé F., et al. (2019). Precision medicine in obstructive sleep apnoea. *Lancet Respir. Med.* **7**:456–464. DOI:10.1016/S2213-2600(19)30044-X
5. Schweitzer P.K., Taranto-Montemurro L., Ojile J.M., et al. (2023). The combination of aroxybutynin and atomoxetine in the treatment of obstructive sleep apnea (MARIPOSA): A randomized controlled trial. *Am. J. Respir. Crit. Care Med.* **208**:1316–1327. DOI:10.1164/rccm.202306-1036OC

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AUTHOR CONTRIBUTIONS

All authors conceived the original idea, wrote and reviewed the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.