Title:
Combination of atomoxetine with the novel antimuscarinic aroxybutynin improves mild to moderate OSA

Introduction:
OSA remains a common and serious sleep disorder affecting approximately 20 million people in the United States (US). Despite advances in CPAP therapy, considered a first line treatment, acceptance and adherence rates continue to be challenging.

Muscle hypotonia is a major contributor to OSA pathogenesis. Loss of pharyngeal muscle activity during NREM sleep is believed to be secondary to loss of norepinephrine (NE) stimulation and, during REM sleep, secondary to muscarinic inhibition. Combining drugs that increase NE activation and minimize muscarinic inhibition has shown some efficacy in treating OSA. This study assessed atomoxetine plus a novel antimuscarinic drug, aroxybutynin, on OSA severity.

Previous pharmacological treatment studies of OSA suggested that the combination of atomoxetine and oxybutynin is safe and effective. The current study is with aroxybutynin (combination designated AD-109), a new enantiomerically pure form of oxybutynin which is proposed to have an improved safety and efficacy profile in OSA compared to racemic oxybutynin.

Materials and Method:
This was a randomized, double-blind, placebo-controlled, multisite, crossover design study of 30 patients who met eligibility criteria for mild to moderate OSA. Each received low-dose AD109, high dose AD109, and placebo at bedtime across three overnight periods in a randomized order. Subjects who met all enrollment criteria were randomized to receive the following experimental treatments, one treatment on each of 3 PSG nights, separated by at least a one-week washout period:
• Atomoxetine 75 mg + aroxybutynin 2.5 mg (i.e. 75/2.5)
• Atomoxetine 37.5 mg + aroxybutynin 2.5 mg (i.e. 37.5/2.5)
• Placebo

Dosing of the study treatment occurred immediately prior to lights out. The morning following each PSG, in the crossover period, the DSST, KSS, and sleep quality VAS were administered. Each PSG night was followed by a 1-week washout period.

AE/SAEs were collected at each study visit and by telephone contact with participants during each washout period.

The primary endpoint measure was change in Hypoxic Burden (HB) and key secondary endpoints included Apnea Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI).

Safety endpoints included: physical exam, vital signs, clinical laboratory assessment, spontaneous adverse events including the post-dosing period, DSST and PSG parameters.

Results:
Patients treated with both the high and low doses of AD109 had a large, statistically significant, and clinically meaningful difference from placebo in their Hypoxic Burden (HB), which was the study's primary endpoint. The median HB for participants on placebo was 13.9 (%min)/h as compared to a median of 2.3 (%min)/h for patients on the high dose (p<0.001) and to a median of 7.3 (%min)/h on the low dose (p<0.01). HB measures the total amount of respiratory event-related hypoxemia during sleep. Additionally, the data showed a statistically significant and clinically meaningful median reduction in Apnea-Hypopnea Index (AHI) [Median AHI of 13.2 events/h on placebo reduced to a median of 5.5 events/h on the high dose (p<0.001) and to a median of 7.8 on the low dose (p<0.05)]. AD109 also demonstrated a highly favorable safety profile.

Conclusions:
This study provides further support that a pharmacological intervention for OSA, namely the combination of **atomoxetine and aroxybutynin,** offers promising results. Additional development of this compound and others is warranted.