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Sleep Disorders

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A PER-PROTOCOL ANALYSIS OF PATIENT-REPORTED OUTCOMES IN THE PHASE 3 CLINICAL TRIALS OF AROXYBUTYNIN AND ATOMOXETINE (AD109) IN OSA

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PURPOSE: AD109, an investigational fixed-dose oral anti-apneic neuromuscular modulator, combines the novel antimuscarinic, aroxybutynin (2.5 mg), with the selective norepinephrine reuptake inhibitor, atomoxetine (75 mg) in one tablet. In one of the largest clinical development program for an obstructive sleep apnea (OSA) pharmacotherapy, AD109 significantly improved airway obstruction and oxygenation during sleep in patients with mild-to-severe OSA. We performed an analysis of key secondary endpoints, the patient-reported outcomes (PROs) of the Phase 3 trials of AD109 in OSA in the per-protocol set.

METHODS: SynAIRgy (NCT05813275; 26-week) and LunAIRo (NCT05811247; 51-week) were randomized, double-blind, placebo (PBO)-controlled, parallel-arm trials of AD109 in adults with mild-to-severe OSA who were intolerant to or refused positive airway pressure therapy. Key inclusion criteria required an apnea-hypopnea index >5 events/hr (4% hypopnea desaturation), Patient Reported Outcome Measurement Information System (PROMIS)-Fatigue (F) T-score >50 at the first visit, and BMI 18.5–40 kg/m2 for males / 18.5–42 kg/m2 for females. PRO assessments at Week 26 included the PROMIS-F T-score, PROMIS-Sleep Impairment (SI) T-score, and Epworth Sleepiness Scale (ESS). Supportive per-protocol analyses of the pooled PROs were performed, consisting of participants who completed treatment up to Week 26, had ≥70% medication adherence, and no major protocol deviations. Pre-specified subgroups defined by baseline ESS ≥10 and PROMIS-F T-score ≥58.5 were also analyzed.

RESULTS: A total of N=872 participants (AD109: n=379, PBO: n=493) were included in the per-protocol set for both trials. The mean PROMIS-F T-score improvement at Week 26 was −7.7 with AD109 and −6.6 with PBO, representing an estimated treatment difference (LS mean [95% CI]) of −1.0 points (−2.0, −0.1; P=0.035). The mean PROMIS-SI T-score improvement at Week 26 was −8.5 with AD109 and −7.3 with PBO, representing an estimated treatment difference of −1.3 points (−2.3, −0.2; P=0.017).In participants with baseline excessive daytime sleepiness (ESS ≥10; AD109: n=223; PBO: n=248), the mean PROMIS-F T-score improvement at Week 26 was −9.3 with AD109 and −7.0 with PBO, representing an estimated treatment difference of −2.4 points (−3.7, −1.1; P=0.0004). The mean PROMIS-SI T-score improvement at Week 26 was −10.7 with AD109 and −8.0 with PBO, representing an estimated treatment difference of −2.7 points (−4.1, −1.2; P=0.0004).In participants with baseline excessive symptomatic burden defined by an ESS ≥10 and PROMIS-F T-score ≥58.5 (AD109: n=156; PBO: n=170), the mean PROMIS-F T-score improvement at Week 26 was −11.3 with AD109 and −8.0 with PBO, representing an estimated treatment difference of −3.2 points (−4.9, −1.6; P<0.0001). The mean PROMIS-SI T-score improvement at Week 26 was −12.2 with AD109 and −8.9 with PBO, representing an estimated treatment difference of −3.3 (−5.1, −1.5; P=0.0003).

CONCLUSIONS: AD109 achieved statistically significant improvement in fatigue and sleep-related impairment at Week 26 versus PBO in the per-protocol set. Participants who were more symptomatic at baseline experienced clinically meaningful improvements in symptoms.

CLINICAL IMPLICATIONS: OSA is a heterogenous disease with considerable variability in the presence and severity of symptomatic burden. This analysis indicates that those OSA participants having elevated symptomatic burden at baseline and remaining on treatment may experience greater symptomatic improvement with AD109.

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