phoenix CHEST 2026 October 18-21

Late-Breaking

SESSION TITLE: Late-Breaking Scientific Abstract Posters (B): Pulmonary Vascular Disease, Sleep Disorders
SESSION TYPE: Original Investigation Posters
PRESENTED ON: 10/20/2026 01:45 pm - 02:30 pm

BASELINE HYPOXIC BURDEN AS A POTENTIAL MARKER OF BLOOD PRESSURE RESPONSE TO AROXYBUTYNIN AND ATOMOXETINE (AD109) IN OBSTRUCTIVE SLEEP APNEA

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PURPOSE: Obstructive sleep apnea (OSA) is associated with increased cardiovascular risk, including hypertension. Hypoxic burden (HB) has emerged as a stronger predictor of cardiovascular risk as compared to the apnea-hypopnea index. AD109, an investigational neuromuscular modulator that combines aroxybutynin (2.3 mg) and atomoxetine (75 mg) improves both apnea severity and HB in Phase 3 trials. Given the mechanistic link between nocturnal hypoxemia and blood pressure (BP) regulation, HB may identify patients most likely to experience blood pressure benefit from AD109 treatment.

METHODS: This exploratory analysis was performed in the pooled safety set (randomized participants who received ≥1 dose of study drug) from the Phase 3 SynAIRgy and LunAIRo trials of AD109 in OSA. Morning systolic BP (SBP) and diastolic BP (DBP) at Week 26 were evaluated. Treatment effects and moderation by baseline hypoxic burden (HB_4), defined as the total area under the oxygen desaturation curve across respiratory events meeting the 4% desaturation criterion and normalized by total sleep time (%·min/hr), were assessed using pooled ANCOVA models that included a treatment-by-log(HB_4) interaction, adjusted for baseline BP, age, BMI, and study. Additional analyses assessed effect modification by HB_4 in sex-specific subgroups.

RESULTS: In the pooled safety set (N=1,299; mean age, 57.2 ± 10.7 years; 616 women and 683 men), mean baseline morning SBP and DBP were 126.2 ± 11.0 mmHg and 80.3 ± 7.6 mmHg, and mean baseline HB_4 was 61.3 ± 62.6 %·min/hour (3.8 ± 0.8 log-transformed).

Among participants assigned to placebo, each 1-unit higher log(HB_4) at baseline was associated with greater increases in morning SBP (1.37 mmHg; 95% CI: 0.16, 2.59) and DBP (0.86 mmHg; 95% CI: 0.08, 1.64) at Week 26.

In contrast, AD109 treatment altered the BP trajectory associated with higher baseline HB_4. For each 1-unit increase in log (HB_4), the corresponding changes in morning SBP and DBP were 0.16 mmHg (95% CI: −1.25, 1.58; interaction P=0.20) and 0.70 mmHg (95% CI: −0.21, 1.62; interaction P=0.80), respectively; both non-significant.

The SBP findings were stronger in women (placebo: 2.06 [0.05, 4.08] mmHg per 1-unit log(HB_4); AD109: −1.54 [−3.71, 0.62] mmHg per 1-unit log(HB_4); interaction P=0.016). DBP showed a similar direction in women (placebo: 1.27 [0.03, 2.50] mmHg; AD109: 0.36 [−0.97, 1.69] mmHg per 1-unit log(HB_4)) but the interaction was not significant (interaction P=0.322). No evidence of effect modification by baseline HB_4 was seen in men for SBP (interaction P=0.495) or DBP (interaction P=0.444).

CONCLUSIONS: In this exploratory pooled analysis of the SynAIRgy and LunAIRo Phase 3 trials, higher baseline HB_4 was associated with an increase in morning SBP over 26 weeks among placebo-treated participants. In contrast, this association appeared attenuated in the AD109 arm, with no net rise in morning SBP. This effect modification was more pronounced and statistically significant in women, though the pooled interaction did not reach significance.

CLINICAL IMPLICATIONS: These hypothesis-generating findings suggest baseline HB_4 may help identify OSA patients, particularly women, whose blood pressure trajectory is most favorably influenced by AD109.

DOI: https://doi.org/10.1016/j.chest.2026.09.033

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