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Impact of AXS-12 on Symptom Severity and Functional Impairment in Narcolepsy: Results from the Phase 3 SYMPHONY Trial

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Key Objective

- To evaluate the effect of AXS-12 (reboxetine) on symptom severity, daily functioning, and mood in the Phase 3 SYMPHONY trial of AXS-12 in narcolepsy

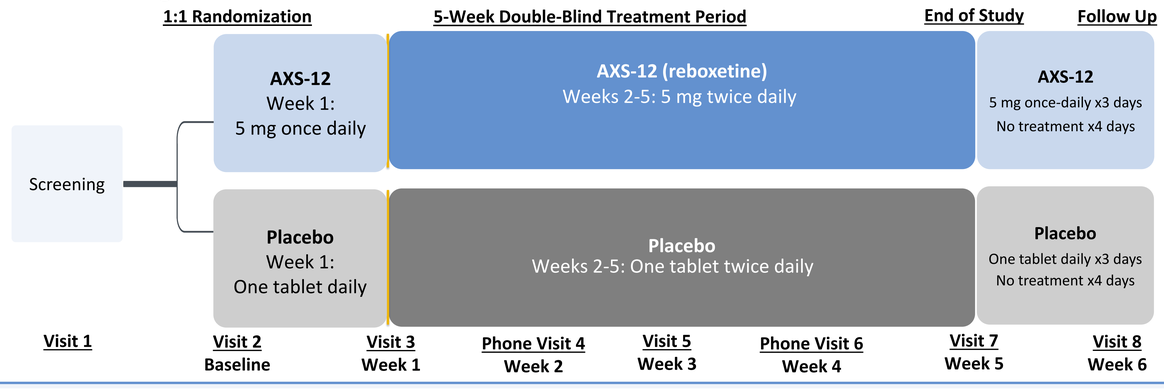
Introduction

- Narcolepsy is a chronic neurologic condition associated with severe symptom burden, impaired functioning, and reduced quality of life[1]
  - Comorbid mood disorders, such as anxiety and depression, are also common and can further impact daily life[2]
- Most patients require pharmacotherapy, yet despite available options, often continue to experience burdensome symptoms which impair daily functioning, reduce productivity, and diminish quality of life[2]
- AXS-12 (reboxetine) is a selective norepinephrine reuptake inhibitor and cortical dopamine modulator[3] under investigation for the treatment of narcolepsy
- In the Phase 3 SYMPHONY trial, AXS-12 met the primary endpoint, a statistically significant reduction in weekly cataplexy attacks from baseline to Week 5 versus placebo[4]
  - Additionally, AXS-12 improved both excessive daytime sleepiness and subjective cognitive function
- Here, we report secondary endpoints assessing symptom severity, daily functioning, and mood

Methods

- SYMPHONY was a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial, conducted across approximately 60 sites in the US and Canada. Ninety participants with a diagnosis of NT1 were enrolled
- Following a screening period, participants were randomized 1:1 to treatment with AXS-12 (reboxetine) or placebo for 5 weeks, then completed a 1-week follow-up (**Figure 1**)
- Key eligibility criteria:
  - Diagnosis of NT1 with ≥7 cataplexy attacks/week, or ≥14 across 2 weeks
  - Aged 15-75 years
  - Concurrent use of modafinil/armodafinil was allowed if dose was stable for ≥3 weeks before trial treatment and maintained through the trial duration
  - Concurrent use of other medications used to treat narcolepsy was prohibited
  - Diagnosis of another clinically significant condition potentially causing EDS was exclusionary

Figure 1. Trial Design



Select Secondary Endpoints

The effect of AXS-12 compared to placebo was evaluated on each of the following outcomes at Week 5:

- **Clinical Global Impression of Change-Severity (CGI-S) for Narcolepsy Overall:** Clinician-rated measure of overall symptom severity
  - Scored from 1 (normal) to 7 (severely ill)
- **Functional Outcomes of Sleep (FOSQ)-10:** Patient-reported measure of the impact of excessive daytime sleepiness on daily functioning across five subscales, scored from 1 (extreme difficulty) to 4 (no difficulty)
  - Total scores range from 5 to 20, with higher scores indicating better functioning
- **EuroQoL 5-Dimension 5-Level (EQ-5D-5L):** Patient-reported assessment of health-related quality of life across five domains, each scored from 1 (no problems) to 5 (extreme problems)
  - Only results of the Anxiety/Depression domain are reported
  - **Anxiety/depression domain:** (1 = no anxiety/depression, 5 = extreme anxiety/depression)

Results

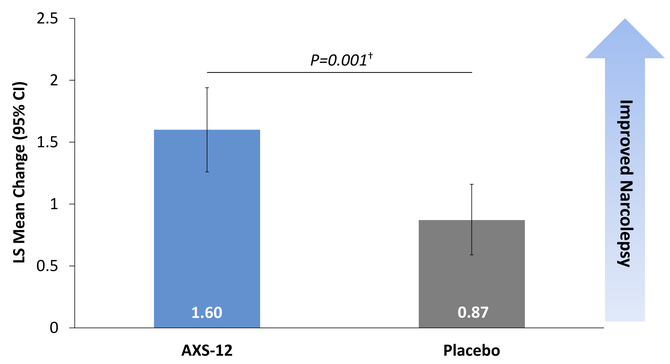
Participants

Table 1. Baseline Sociodemographic and Clinical Characteristics	AXS-12 (N=46)	Placebo (N=44)
Age, mean (SD), years	36.0 (13.4)	34.2 (12.1)
Sex, female, n (%)	25 (54.3)	29 (65.9)
Race, n (%)		
White	27 (58.7)	28 (63.6)
Black or African American	13 (28.3)	11 (25.0)
Asian	1 (2.2)	2 (4.5)
Other	2 (4.3)	1 (2.3)
BMI, mean (SD)	29.7 (6.3)	27.4 (5.6)
Time since diagnosis, mean (SD), years	7.9 (9.0)	6.3 (7.0)
Weekly frequency of cataplexy attacks, median	19.3	21.6
Epworth Sleepiness Scale score, mean (SD)	18.3 (3.1)	17.3 (3.3)
CGI-S for Narcolepsy Overall, mean (SD)	5.2 (1.0)	4.9 (1.0)
EQ-5D-5L, ≥ slightly anxious/depressed, %	47.8	45.5
FOSQ-10, mean (SD)	11.1 (3.1)	11.6 (3.2)
Use of modafinil or armodafinil, %	32.6	29.5

- Baseline characteristics were balanced between both arms

BMI, body mass index; CGI-S, Clinical Global Impression of Severity; EDS, excessive daytime sleepiness; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FOSQ-10, Functional Items of Sleep Questionnaire-10.

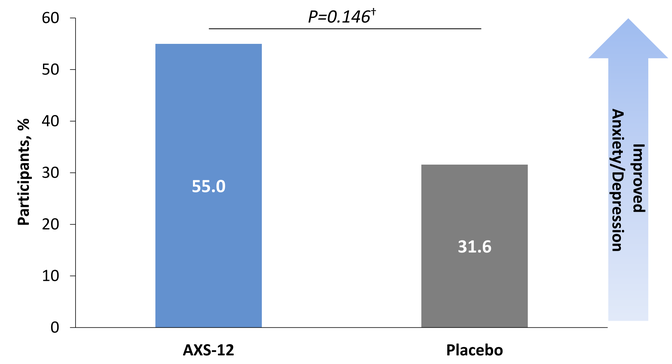
Figure 2. CGI-S for Narcolepsy Overall



- AXS-12 led to a greater improvement in CGI-S score at Week 5 compared to placebo

CGI-S, Clinical Global Impression of Severity; LS, least squares.
†Nominal p-value.

Figure 3. EQ-5D-5L Anxiety/Depression

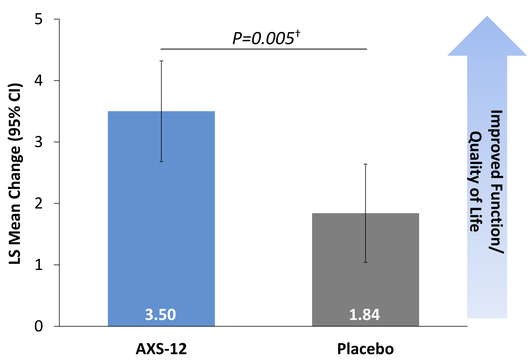


- A numerically greater proportion of participants achieved improvements on the anxiety/depression domain with AXS-12 versus placebo at from baseline to Week 5*

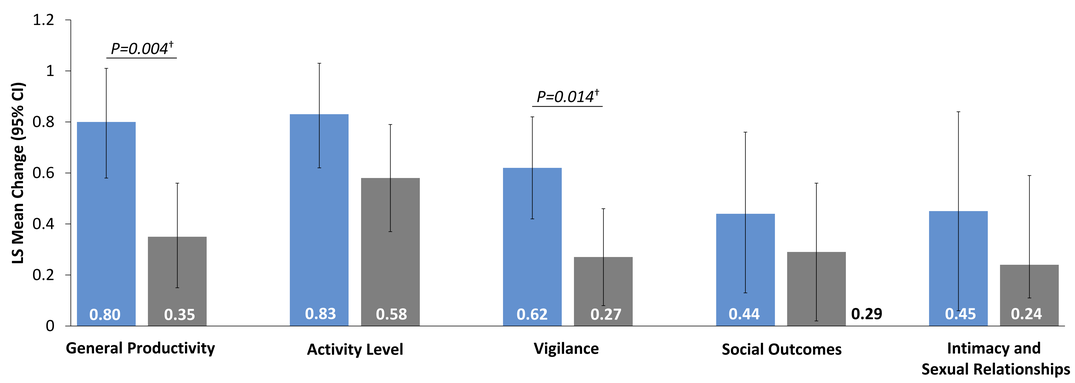
EQ-5D-5L, EuroQol 5-Dimension, 5-Level.
†Nominal p-value. *Improvement defined as a >=1-level reduction from baseline to Week 5.

Figure 4. FOSQ-10

A. LS Mean Change in FOSQ-10 Total Score From Baseline to Week 5



B. LS Mean Change in FOSQ-10 Subscales From Baseline to Week 5



- AXS-12 led to a greater improvement in FOSQ-10 total score at Week 5 compared to placebo
- AXS-12 led to nominally significant improvements in the General Productivity and Vigilance subscales of the FOSQ-10, and to numerically larger improvements in the Activity Level, Social Outcomes, and Intimacy and Sexual Relationships subscales

FOSQ-10, Functional Items of Sleep Questionnaire-10; LS, least squares; ns, not significant.
†Nominal p-value.

Baseline values of subscales (AXS-12 vs. placebo): General Productivity: (2.1 vs. 1.9); Activity Level: (1.9 vs. 1.9); Vigilance (2.0 vs. 2.3); Social Outcomes (2.5 vs. 2.6); Intimacy and Sexual Relationships (2.2 vs. 2.6).

Safety and Tolerability

- The most common TEAEs in the AXS-12 arm were dry mouth (n=6, 13.0%), nausea (n=6, 13.0%), constipation (n=4, 8.7%), paresthesia (n=4, 8.7%), and decreased appetite (n=3, 6.5%); all were mild-to-moderate
- The rates of discontinuation due to AEs were low (n=1 in each of AXS-12 [2.2%] and placebo [2.3%] arms)
- There were no serious AEs in either arm

Conclusions

- AXS-12 demonstrated a reduction in the clinical impression of overall narcolepsy symptom severity compared to placebo
- AXS-12 improved mood-related symptoms, with more participants reporting reduced anxiety/depression than with placebo
- AXS-12 improved daily functioning impaired by excessive daytime sleepiness, particularly in productivity and vigilance domains, and with numerical superiority to placebo across all other domains
- Combined with prior findings on cataplexy and cognitive function, as well as favorable safety/tolerability, these results support the potential of AXS-12 as a therapeutic option addressing multiple burdensome symptoms of narcolepsy

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Disclosures

M. Thorpy serves as a consultant to Axsome Therapeutics.
L. Krahn serves as a consultant to Axsome Therapeutics.
R. Bogan serves as a consultant to Axsome Therapeutics, Avadel, Harmony, Jazz Pharmaceuticals, and Takeda and is on the speakers bureau for Axsome Therapeutics, Harmony, Idorsia, and Jazz Pharmaceuticals.
B Corser serves as a speaker for Jazz Pharmaceuticals and Axsome Therapeutics; a consultant to Harmony Biosciences; and an investigator for Jazz Pharmaceuticals, Centessa, Harmony Biosciences, Eli Lilly, Mineralys, Alkermes, Eisai, and Avadel.
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