AXS-12 for the Treatment of Narcolepsy: Topline Results From the Phase 3 SYMPHONY Trial

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Key Question

- Does AXS-12 reduce the frequency of cataplexy attacks and improve other symptoms of narcolepsy type 1 in the Phase 3 randomized controlled trial (SYMPHONY)?

Conclusions

- AXS-12 met its primary endpoint, by significantly reducing weekly cataplexy attacks compared to placebo
- In addition to reducing cataplexy, AXS-12 improved both excessive daytime sleepiness and subjective cognitive function, highlighting the potential for AXS-12 to impact multiple symptoms of narcolepsy
- AXS-12 was generally well-tolerated and discontinuations due to adverse events were uncommon; safety signals were consistent with the Phase 2 CONCERT trial
- The results of the Phase 3 SYMPHONY trial were consistent with the positive Phase 2 trial and highlight the positive therapeutic impact of AXS-12 on persons with narcolepsy, who experience a substantial burden of disease;[6] additional analyses are ongoing

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Disclosures

MJT serves as a consultant to Axsome Therapeutics.
LK serves as a consultant to Axsome Therapeutics.
RB 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.
BC 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.
AC, EBL, and **HT** are current employees of Axsome Therapeutics.

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Introduction

- Narcolepsy is a chronic neurological disorder that causes dysregulation of the sleep-wake cycle, characterized clinically by excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nocturnal sleep[1,2]
- People with narcolepsy type 1 (NT1) experience cataplexy, a sudden weakening or complete loss of muscle tone while awake, usually triggered by intense emotions such as laughter, fear, anger, stress, or excitement
  - Approximately 70% of individuals with narcolepsy experience cataplexy[3]
- AXS-12 (reboxetine) is a highly selective and potent norepinephrine reuptake inhibitor and cortical dopamine modulator[4] under development for the treatment of narcolepsy
- AXS-12 regulates noradrenergic activity, which helps maintain muscle tone during wakefulness, and is thought to modulate both noradrenergic and dopaminergic pathways to stabilize sleep-wake states, enhance alertness, and improve cognition[5]
- In the Phase 2, crossover, placebo-controlled CONCERT trial, AXS-12 met all primary and key secondary endpoints, demonstrating statistically significant reductions in cataplexy frequency and EDS, improved subjective sleep quality and cognitive function; additionally, AXS-12 was safe and well-tolerated[5]
- The objective of the SYMPHONY Phase 3 trial was to assess the efficacy and safety of AXS-12 compared to placebo for treating cataplexy in narcolepsy

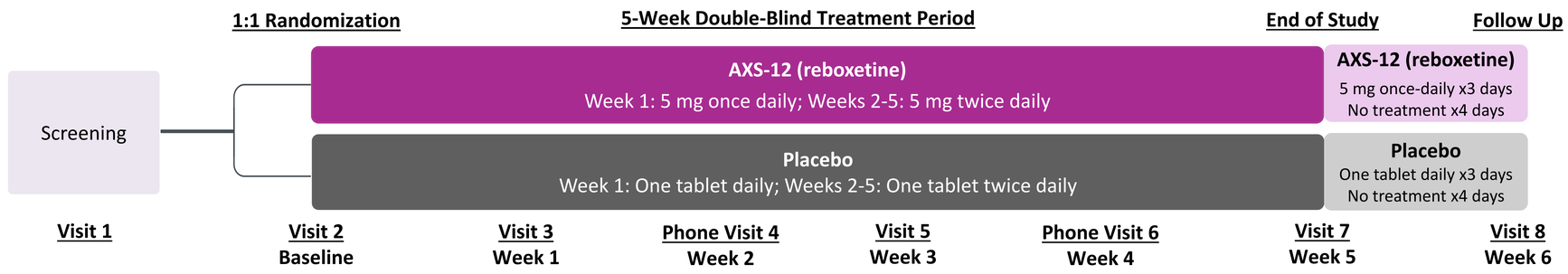
Methods & Trial Design

- SYMPHONY was a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial, conducted across ~60 sites in the US and Canada in participants with a diagnosis of NT1
- 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
  - Diagnosis of another clinically significant condition potentially causing EDS was exclusionary

Trial Endpoints

- Primary endpoint: Change from Baseline to Week 5 in the weekly frequency of cataplexy attacks, defined as (AXS-12 Week 5/AXS-12 Baseline)/(Placebo Week 5/Placebo Baseline)
- Secondary endpoints included (all assessed at Week 5):
  - Percentage of participants with cataplexy remission (100% reduction in weekly attacks)
  - Percentage of cataplexy free days per week
  - Change in frequency of participant-reported inadvertent naps or sleep attacks as assessed by the Narcolepsy Symptom Assessment Questionnaire (NSAQ)
  - Change in Clinical Global Impression of Severity (CGI-S) for EDS score
  - Change in the cognitive items of the Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10) score
- Evaluation of additional endpoints is ongoing and may be included in future scientific presentations

Figure 1. Trial Design



Key Findings

Table 1. Baseline Sociodemographic and Clinical Characteristics

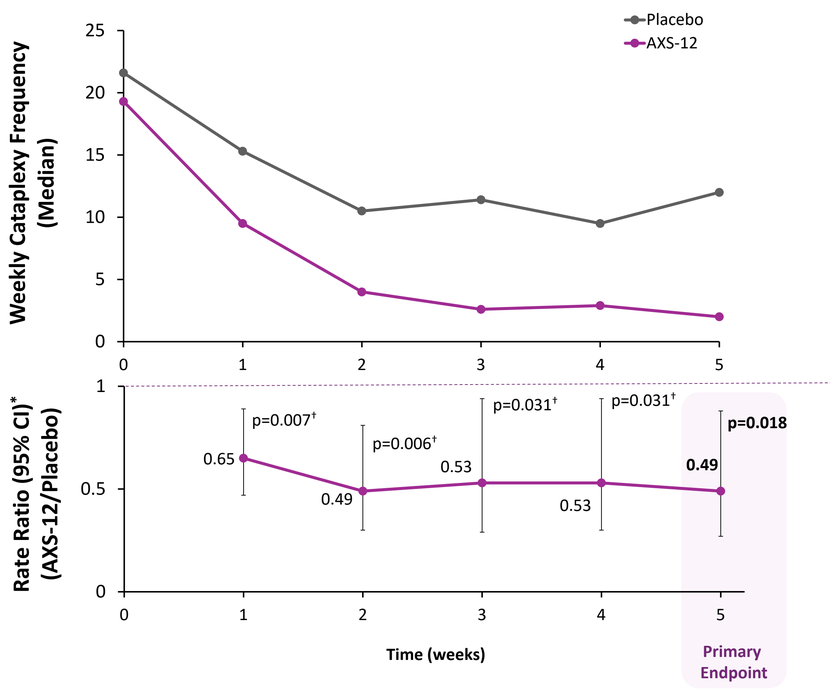
	AXS-12 (N=46)	Placebo (N=44)
Age, mean (SD), years	36.0 (13.4)	34.2 (12.1)
Sex, female, n (%)	25 (54.3)	29 (65.9)
Race, n (%)		
White	27 (58.7)	28 (63.6)
Black or African American	13 (28.3)	11 (25.0)
Asian	1 (2.2)	2 (4.5)
Other	2 (4.3)	1 (2.3)
BMI, mean (SD)	29.7 (6.3)	27.4 (5.6)
Time since diagnosis, mean (SD), years	7.9 (9.0)	6.3 (7.0)
Weekly frequency of cataplexy attacks, median	19.3	21.6
CGI-S for EDS, mean (SD)	5.3 (0.9)	5.1 (1.0)
Epworth Sleepiness Scale score, mean (SD)	18.3 (3.1)	17.3 (3.3)
Use of modafinil or armodafinil, %	32.6	29.5

BMI, body mass index; CGI-S, Clinical Global Impression of Severity; EDS, excessive daytime sleepiness.

- The study population comprised 90 participants; baseline sociodemographic and clinical characteristics were similar across both treatment groups (**Table 1**)

Primary Endpoint: Frequency of Cataplexy Attacks

Figure 2. Change in Weekly Frequency of Cataplexy Attacks

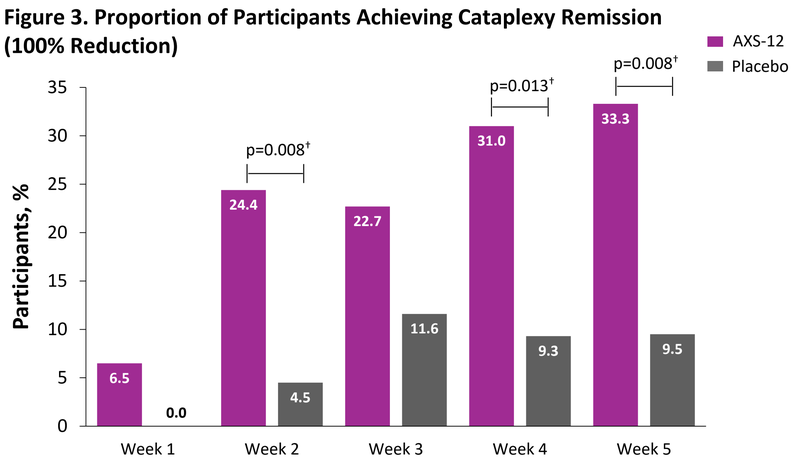


- AXS-12 demonstrated a consistent reduction from baseline in median weekly cataplexy frequency compared to placebo (**Figure 2, top panel**)
- AXS-12 met the primary endpoint, a statistically significant reduction in weekly cataplexy attacks from baseline to Week 5 (rate ratio=0.49; p=0.018) (**Figure 2, bottom panel**)
  - Mean percent reductions in weekly cataplexy attacks from baseline to Week 5 were 83% with AXS-12 and 66% with placebo
  - Greater reductions in weekly cataplexy attacks were observed as early as Week 1 with AXS-12 compared to placebo (rate ratio=0.65, p=0.007)

*Rate Ratio: For both placebo and AXS-12 groups, the ratio of the weekly frequency of cataplexy attacks post-treatment to baseline is taken; the rate ratio is the ratio of these values. A rate ratio less than 1 indicates fewer attacks with AXS-12 compared to placebo.
†Nominal p-value.

Secondary Endpoint: Cataplexy Remission

Figure 3. Proportion of Participants Achieving Cataplexy Remission (100% Reduction)

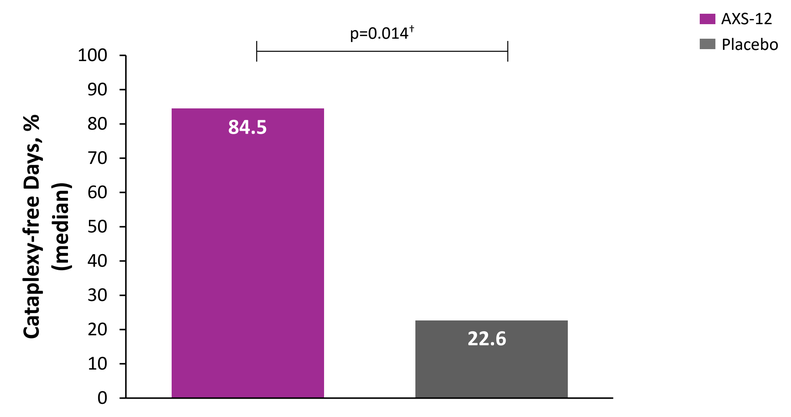


†Nominal p-value.

- Rates of cataplexy remission (defined as 100% reduction from baseline) at Week 5 were improved with AXS-12 (33.3%) compared to placebo (9.5%; p=0.008) (**Figure 3**)

Secondary Endpoint: Cataplexy-Free Days

Figure 4. Cataplexy-Free Days at Week 5

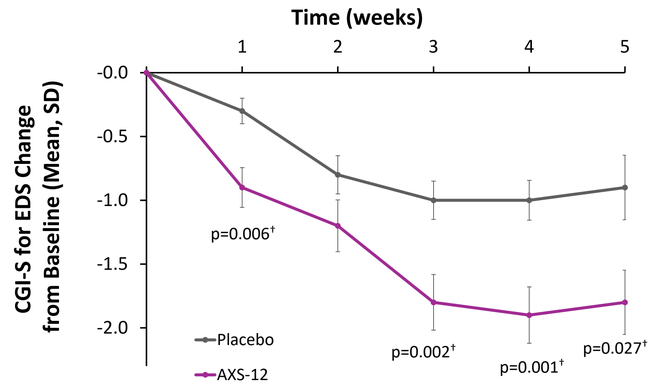


†Nominal p-value.

- AXS-12 increased the percentage of cataplexy-free days per week (days with zero cataplexy attacks) relative to placebo (median 84.5% vs 22.6%; p=0.014) (**Figure 4**)

Secondary Endpoints: Excessive Daytime Sleepiness (EDS)

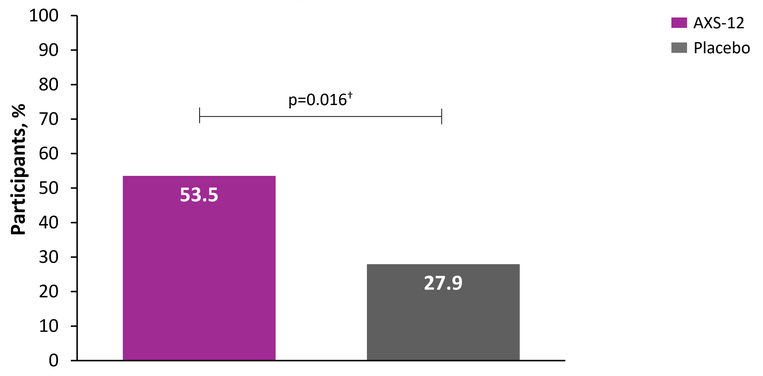
Figure 5. Change in Clinical Global Impression of Severity (CGI-S) for EDS



†Nominal p-value.

- AXS-12 reduced EDS severity at Week 5, assessed by the CGI-S, with mean reductions of 1.8 points for AXS-12 and 0.9 points for placebo (p=0.027) (**Figure 5**)
  - Greater reductions in EDS were observed with AXS-12 compared to placebo as early as Week 1, and at all timepoints through Week 5

Figure 6. Proportion of Participants Achieving Reduction in Inadvertent Naps or Sleep Attacks

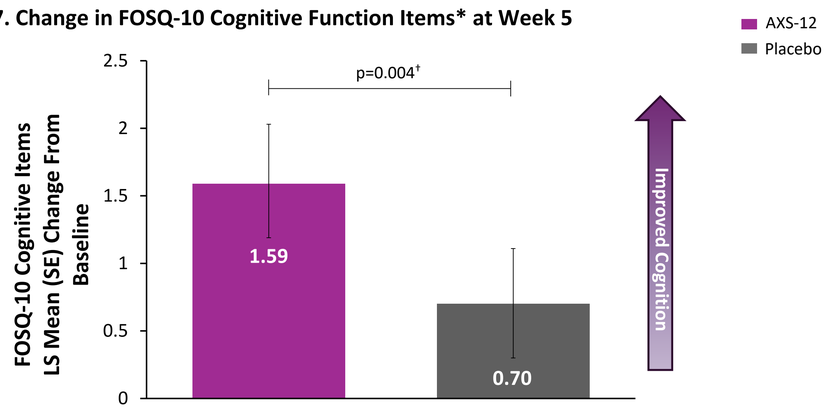


†Nominal p-value.

- A higher proportion of participants in the AXS-12 arm (53.5%) reported reductions in inadvertent naps or sleep attacks on the NSAQ at Week 5 compared to those in the placebo arm (27.9%; p=0.016) (**Figure 6**)

Secondary Endpoint: Subjective Cognitive Function

Figure 7. Change in FOSQ-10 Cognitive Function Items* at Week 5



*Total score of 2 questions: 1. "Do you have difficulty concentrating because you are sleepy or tired?" and 2. "Do you have difficulty remembering things because you are sleepy or tired?"
†Nominal p-value.

- AXS-12 improved concentration and memory as measured by the cognitive function items on the FOSQ-10 at Week 5 (LS mean change 1.59 vs. 0.70; p=0.004) (**Figure 7**)

Safety and Tolerability

- The most commonly reported adverse events in the AXS-12 arm (≥ 5%) 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%), which were overall mild to moderate
- The rates of discontinuation due to adverse events were low (n=1 in each of AXS-12 [2.2%] and placebo [2.3%] arms)
- There were no serious adverse events in either arm