ENCORE: Topline Results of a Phase 3 Open-label Extension and Randomized-Withdrawal Study of AXS-12 in Narcolepsy

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Key Objective

- To examine the long-term efficacy and safety of AXS-12 with open-label treatment and maintenance of effect during double-blind withdrawal in the Phase 3 ENCORE study in participants with narcolepsy and cataplexy

Introduction

- Narcolepsy is a chronic neurological disorder that causes dysregulation of the sleep-wake cycle[1]
- Approximately 70% of individuals with narcolepsy experience cataplexy (narcolepsy type 1), a sudden weakening or complete loss of muscle tone while awake, usually triggered by intense emotions, such as laughter, fear, anger, stress, or excitement[2-4]
- AXS-12 (reboxetine) is a highly selective norepinephrine reuptake inhibitor and cortical dopamine modulator under development for narcolepsy[5]
- 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[6]
- In the Phase 3 SYMPHONY study, AXS-12 met the primary endpoint and demonstrated improvements in cataplexy, excessive daytime sleepiness (EDS), and cognitive function, and was safe and well tolerated[6]

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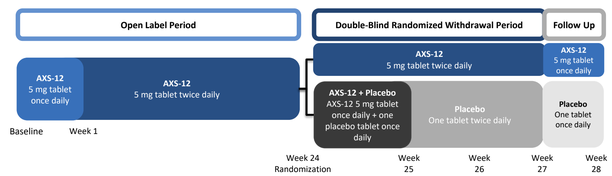
Disclosures
R.K. Bogan serves as a consultant to Axsome Therapeutics, Avadel, Harmony, Jazz Pharmaceuticals, and Takeda and is on the speakers bureau for Axsome Therapeutics, Harmony, Idorsia, and Jazz Pharmaceuticals.
M.J. Thorpy serves as a consultant to Axsome Therapeutics.
L.E. Krahn serves as a consultant to Axsome Therapeutics.
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.
C. Shapiro serves as a consultant to Axsome Therapeutics.
D. Chen, A. Chhabra, and **H. Tabuteau** are current employees of Axsome Therapeutics.
E.B. Leary is a former employee of Axsome Therapeutics

Methods

- ENCORE was a multicenter, Phase 3 study comprising 2 periods, a 6-month open-label treatment period (OLP), followed by a 3-week double-blind, randomized-withdrawal period (DBRWP)
- Eligible participants had narcolepsy type 1 with symptoms of cataplexy and EDS who had previously completed the 5-week Phase 3 SYMPHONY study
  - Participants rolled over to ENCORE directly after completing the SYMPHONY study
- Here we report cataplexy outcomes including change in weekly frequency of cataplexy attacks, cataplexy response, and change in cataplexy-free days per week during the OLP, and the change from randomization in weekly frequency of cataplexy attacks during the DBRWP; safety and tolerability during both periods are also reported

Figure 1. Study Design

- Participants were evaluated every 4 weeks during the OL period, with an additional remote visit at week 2
- Participants who completed the OL were randomized 1:1 to continue twice-daily AXS-12 or switch to once-daily AXS-12 plus placebo for 1 week, then placebo twice-daily for 2 weeks
- **Primary endpoint:** Change from randomization in the weekly frequency of cataplexy attacks compared to placebo at week 3 of the DBRWP



Conclusions

- AXS-12 demonstrated long-term efficacy over 6 months in participants who completed the OL period
- During the DBRWP, those who switched to placebo demonstrated a significant worsening in the frequency of cataplexy attacks relative to continued AXS-12 treatment, suggesting a loss of clinical effect in the placebo group
- AXS-12 was well tolerated with no new safety signals detected
- The results of the Phase 3 ENCORE study coupled with the results of the Phase 3 SYMPHONY study, support the positive therapeutic impact of AXS-12 for narcolepsy with cataplexy

Results

Participants

Table 1. Baseline Sociodemographic and Clinical Characteristics for ENCORE Participants

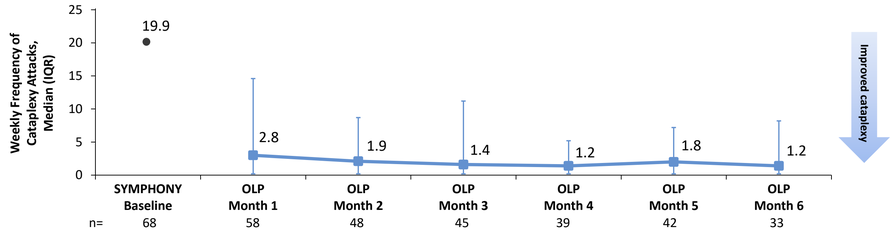
	OLP (N=68)	DBRWP (N=42)
Age, years, mean (SD)	36.3 (13.2)	36.5 (13.1)
Sex, female, n (%)	41 (60)	26 (62)
Race, n (%)		
White	39 (57)	24 (57)
Black or African American	23 (34)	15 (36)
Asian	3 (4)	1 (2)
Other	2 (3)	1 (2)
Multiple	1 (1)	1 (2)
BMI, kg/m^2, mean (SD)	28.6 (6.0)	28.8 (5.6)
Years since diagnosis, mean (SD)	6.6 (7.4)	6.0 (7.4)
Weekly frequency of cataplexy attacks pretreatment (SYMPHONY baseline), median	19.9	19.5

- A total of 68 participants rolled over from the SYMPHONY Phase 3 study and enrolled in the open-label period of ENCORE
- 42 completed the OLP and entered the DBRWP (AXS-12, n=22; placebo, n=20)
  - Overall baseline characteristics were similar between those who entered the study and those who were randomized

BMI, body mass index; DBRWP, double-blind randomized withdrawal period; OLP, open-label period; SD, standard deviation.

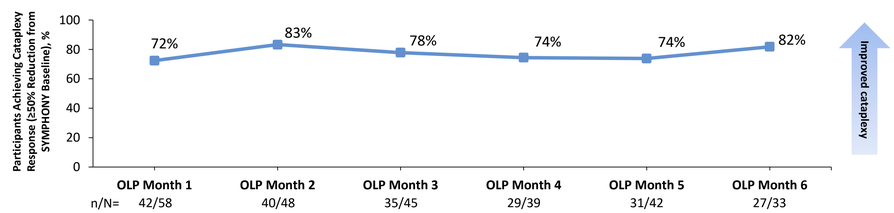
Open Label Period

Figure 2. Weekly Frequency of Cataplexy Attacks at Pretreatment Baseline and During the OLP



- The frequency of weekly cataplexy attacks decreased from a median of 19.9 at the baseline of SYMPHONY to 2.8 and 1.2 at 1 and 6 months, respectively

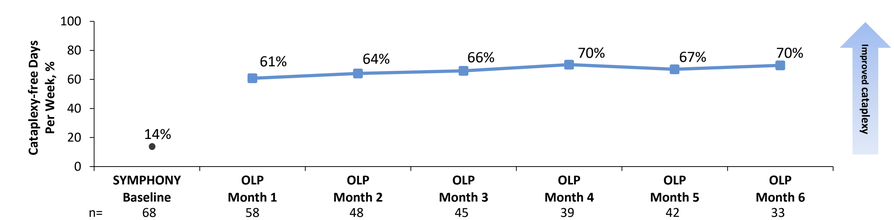
Figure 3. Percentage of Participants Achieving Cataplexy Response[a] in the OLP



[a]Defined as ≥50% reduction from SYMPHONY baseline, measured weekly. Achievement at the end of each month shown.
n/N= the number of responders/the number of participants with data at that timepoint.

- Participants receiving AXS-12 showed a consistent cataplexy response, with 72% and 82% achieving ≥50% reduction from SYMPHONY baseline at 1 and 6 months, respectively

Figure 4. Percentage of Cataplexy-free Days[a] Per Week at Pretreatment Baseline and During the OLP

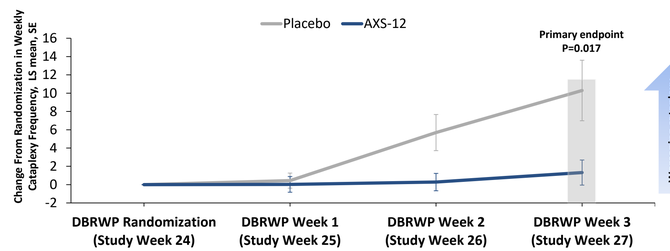


[a]Defined as days with zero cataplexy attacks, measured weekly. Achievement at the end of each month shown.

- AXS-12 increased the mean percentage of cataplexy-free days per week from 14% at SYMPHONY baseline to 61% and 70% at 1 and 6 months, respectively

Double-Blind Randomized Withdrawal Period

Figure 5. Primary Endpoint: Change in Frequency of Cataplexy Attacks During DBRWP



- At DBRWP randomization (after 24 weeks of open-label AXS-12 use), mean weekly frequency of cataplexy attacks was 4.2 for participants randomized to AXS-12 and 6.9 for participants randomized to placebo
- Participants randomized to placebo and who completed the 3-week DBRWP experienced significant worsening with a least squares mean increase of 10.29 weekly cataplexy attacks versus 1.32 for AXS-12 from the start of the (P = 0.017)

DBRWP, double-blind, randomized-withdrawal period; LS, least squares; SE , standard error.

Safety and Tolerability

Table 2. Treatment-emergent Adverse Events (TEAEs)

	OLP	DBRWP	
	AXS-12 Overall (n=68)	AXS-12 (n=22)	Placebo (n=20)
Participants with ≥1 TEAE, n (%)	38 (55.9)	4 (18.2)	5 (25.0)
Participants with ≥1 SAE, n (%)	2 (2.9)	0	0
TEAEs leading to discontinuation, n (%)	12 (17.6)	0	1 (5.0)
TEAEs occurring in ≥5% of participants, n (%)			
Nausea	4 (5.9)	0	0
Tachycardia	4 (5.9)	0	0
Alanine aminotransferase increased	0	0	2 (10.0)
Liver function test increased	0	0	1 (5.0)

- In the OLP, no individual AE led to discontinuation by more than 1 participant
- During the DBRWP, the rates of treatment-related TEAEs were 4.5% in the AXS-12 group and 15.0% in the placebo group
- No new safety signals were noted

DBRWP, double-blind, randomized-withdrawal period; OLP, open-label period; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- AXS-12 demonstrated long-term efficacy over 6 months in participants who completed the OL period
- During the DBRWP, those who switched to placebo demonstrated a significant worsening in the frequency of cataplexy attacks relative to continued AXS-12 treatment, suggesting a loss of clinical effect in the placebo group
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