Neuroscience Education Institute Fall Congress
Nov 5-8, 2026
Colorado Springs, CO, USA

Cognitive and Functional Outcomes From the Phase 3 Open-Label Extension and Randomized-Withdrawal ENCORE Study of AXS-12 in Narcolepsy with Cataplexy

Bruce C. Corser,[1] Michael J. Thorpy,[2] Lois E. Krahn,[3] Richard K. Bogan,[4] Colin Shapiro,[5] Dan Chen,[6] Angad Chhabra,[6] Herriot Tabuteau[6]

[1]Intrepid Research, Cincinnati, OH, United States, [2]Montefiore Medical Center, Sleep-Wake Disorders Center, Bronx, NY, United States, [3]Mayo Clinic College of Medicine, Department of Psychiatry and Psychology, Phoenix, AZ, United States, [4]Medical University of South Carolina, Charleston, SC, United States, [5]Sleep on the Bay, Toronto, Canada, [6]Axsome Therapeutics, Inc., New York, NY, United States

Key Objective

To evaluate the effects of AXS-12 on ability to concentrate, excessive daytime sleepiness, and functional burden over the 24-week open-label treatment period and during the 3-week double-blind withdrawal period in participants with narcolepsy type 1 (NT1)

Introduction

- Narcolepsy is a chronic neurologic disorder that causes dysregulation of the sleep-wake cycle[1] AXS-12 (reboxetine) is a highly selective norepinephrine reuptake inhibitor under development for treatment of narcolepsy[2]
- In the Phase 3 SYMPHONY study, which was 5 weeks in duration, AXS-12 treatment was associated with a significant reduction in weekly cataplexy frequency, as well as improvements in measurements of cognition, excessive daytime sleepiness (EDS), daily function, and overall disease status[3]
- In the Phase 3 long-term ENCORE study, open-label AXS-12 treatment was associated with reductions in weekly cataplexy frequency that were maintained for 24 weeks, followed by loss of effect as indicated by statistically significantly greater increases in weekly cataplexy attacks for subjects switched to placebo compared to those who continued on AXS-12 during the double-blind randomized withdrawal period[4]
- To understand the impact of long-term AXS-12 treatment on NT1 symptoms more broadly, we evaluated secondary endpoints related to EDS, cognition, overall disease status, and work impairment in ENCORE

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 select secondary outcomes **for the OLP**: % of patients with improvement in excessive daytime sleepiness assessed by the Clinic Global Impression of Change [CGI-C] and the PGI-C); % of patients reporting improvement on the ability to concentrate, assessed by the Narcolepsy Symptom Assessment Questionnaire (NSAQ) and the Patient Global Impression of Change (PGI-C); % of patients with improvement in overall narcolepsy status assessed by the CGI-C and the PGI-C); and % impairment while working due to narcolepsy assessed by the Work Productivity and Activity Impairment (WPAI) Questionnaire. **For the DBRWP**, the % of patients with worsening in CGI-C and PGI-C for EDS; the % of patients with worsening on the ability to concentrate, assessed by the NSAQ and the PGI-C; and % of patients with worsening in CGI-C and PGI-C for overall narcolepsy status were assessed.

For a study design schematic and additional details on study design, please scan the QR code

Results

Participants

Table 1. Baseline Sociodemographic and Clinical Characteristics for ENCORE Participants

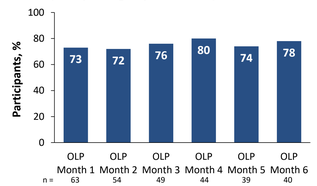
	OLP (N=68)	DBRWP (N=42)
Age, years, mean (SD)	36.3 (13.2)	36.5 (13.1)
Sex, female, n (%)	41 (60)	26 (62)
Race, n (%)		
White	39 (57)	24 (57)
Black or African American	23 (34)	15 (36)
Asian	3 (4)	1 (2)
Other	2 (3)	1 (2)
Multiple	1 (1)	1 (2)
BMI, kg/m^2, mean (SD)	28.6 (6.0)	28.8 (5.6)
Years since diagnosis, mean (SD)	6.6 (7.4)	6.0 (7.4)
Weekly frequency of cataplexy attacks, median[a]	19.9	1.0

- 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 OLP study and those who were randomized in the DBRPW

[a]Baseline frequency for OLP reflects baseline of SYMPHONY trial; baseline frequency for DBRWP reflects median frequency following the OLP and prior to randomization in the DBRWP in ENCORE
BMI, body mass index; DBRWP, double-blind randomized withdrawal period; OLP, open-label period; SD, standard deviation.

Excessive Daytime Sleepiness

Figure 1. Change in EDS: PGI-C



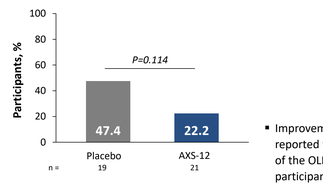
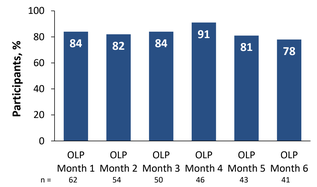
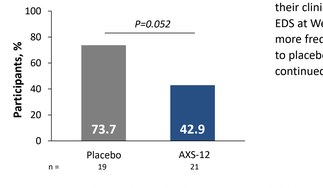


Figure 2. Change in EDS: CGI-C



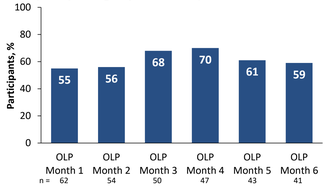


- Improvements in EDS were reported through Month 6 of the OLP by a majority of participants remaining in the trial and their clinicians; among participants who entered the DBRWP and their clinicians, worsening of EDS at Week 3 was reported more frequently after switch to placebo than after continued AXS-12 treatment

[a]Defined as reporting "Minimally" to "Very Much Improved." [b]Defined as reporting "Minimally" to "Very Much Worse."
CGI-C, Clinical Global Impression of Change; DBRWP, double-blind, randomized-withdrawal period; EDS, excessive daytime sleepiness; NSAQ, Narcolepsy Symptom Assessment Questionnaire; OLP, open-label period; PGI-C, Patient Global Impression of Change.

Concentration

Figure 3. Change in Ability to Concentrate: NSAQ Ability to Concentrate Item[a]



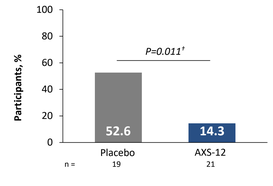
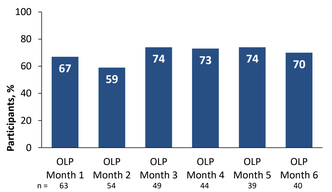
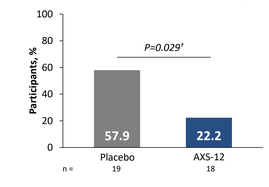


Figure 4. Change in Ability to Concentrate: PGI-C[d]



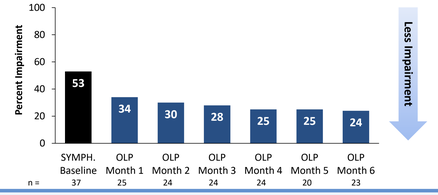


- Improvements in ability to concentrate were reported by a majority of participants remaining in the trial through Month 6 of the OLP; among those who entered the DBRWP, worsening at Week 3 was significantly more frequently reported following switch to placebo than with continued AXS-12 treatment

[a]The Ability to Concentrate item was assessed as part of the NSAQ which evaluates narcolepsy symptoms broadly, not cognition specifically. [b]Defined as reporting "Somewhat Improved" or "Much Improved." [c]Defined as reporting "Somewhat worse" or "Much worse" categories. [d]CGI-C not collected for ability to concentrate. [e]Defined as reporting "Minimally" to "Very Much Improved." [f]Defined as reporting "Minimally" to "Very Much Worse."
DBRWP, double-blind, randomized-withdrawal period NSAQ, Narcolepsy Symptom Assesment Questionnaire; OLP, open-label period; PGI-C, Patient Global Impression of Change. [†]Nominal P-value.

Work Impairment

Figure 5. Impairment While Working Due to Narcolepsy: WPAI

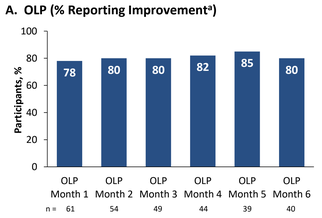


- Throughout the OLP, impairment while working was lower than at SYMPHONY baseline

NT1, narcolepsy type 1; OLP, open-label period; WPAI, Work Productivity and Impairment (Questionnaire).

Overall Narcolepsy Status

Figure 6. Change in Narcolepsy Status: PGI-C



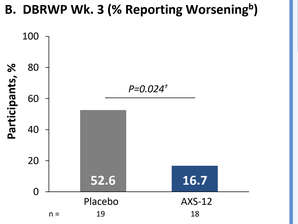
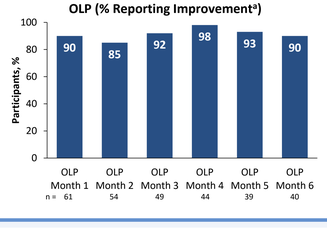


Figure 7. Change in Narcolepsy Status Assessed by CGI-C



- Improvements in overall narcolepsy status were reported by a majority of participants remaining in the trial and their clinicians through Month 6 of the OLP
- Among participants who entered the DBRWP worsening at Week 3 was more frequently reported by participants after switch to placebo than with continued AXS-12 treatment, with a similar clinician-reported findings (placebo: 73.7%; AXS-12 42.9%, p=0.052)

[a]Defined as reporting "Minimally" to "Very Much Improved." [b]Defined as reporting "Minimally" to "Very Much Worse."
CGI-C, Clinical Global Impression of Change; DBRWP, double-blind, randomized-withdrawal period; OLP, open-label period. [†]Nominal P-value.

Safety and Tolerability[a]

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 study discontinuation, n (%)	11 (16.2)	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)[b]
Liver function test increased	0	0	1 (5.0)[b]

- In the OLP, no individual AE led to discontinuation by more than 1 participant[b]
- The most frequently reported TEAEs with AXS-12 (≥5% of subjects) were nausea and tachycardia, which are consistent with its noradrenergic mechanism of action
- No new safety signals were noted

[a]OLP comprised 24 weeks of exposure while DBRWP comprised 3 weeks; also all participants enrolled in DBRWP may have self-selected to some extent based on tolerability
[b]One participant had increased alanine aminotransferase and one participant had increased liver function test on the day of randomization while down-titrating from AXS-12.
DBRWP, double-blind, randomized-withdrawal period; OLP, open-label period; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- Long-term, open-label treatment with AXS-12 was associated with sustained improvements in EDS, concentration and overall NT1 status, as well as reduced work impairment due to NT1
- Discontinuation of AXS-12 due to randomized withdrawal to placebo was associated with worsening EDS, concentration, and overall NT1 status relative to continued AXS-12 treatment, suggesting that therapeutic benefit was maintained with continued treatment through 27 weeks
- These results suggest long-term clinical benefit of AXS-12 in NT1 beyond cataplexy, with no new safety signals observed

References

Chavda V, et al. *Brain Sci*. 2022;12(11):1473.
Hajós M, et al. *CNS Drug Rev*. 2004;10(1):23-44.
Thorpy MJ, et al. Presented at: 27th Congress of the European Sleep Research Society; September 24–27, 2024; Seville, Spain.
Bogan RK, et al. Presented at: 39th Annual Meeting of the Associated Professional Sleep Societies; June 8–11; 2025; Seattle, WA, USA.

Acknowledgments

The authors would like to thank the patients, study investigators, and study staff for their contributions to this research. This study was supported by Axsome Therapeutics,Inc. Under the direction of the authors, Jared Levine, PhD, of Axsome Therapeutics, Inc., provided medical writing and editorial support.

QR Code

Scan the QR code at the top of this poster or access https://www.axsomemedicalaffairs.com/congress-presentations/NEI2026 to view or download a PDF of this poster or access additional information and other Axsome Therapeutics presentations at NEI 2026.

Disclosures

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.
M.J. Thorpy serves as a consultant to Axsome Therapeutics.
L.E. Krahn serves as a consultant to Axsome Therapeutics.
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.
C. Shapiro serves as a consultant to Axsome Therapeutics.

D. Chen, A. Chhabra, and **H. Tabuteau** are current employees of Axsome Therapeutics.