

WELCOME

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

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Introduction

- Narcolepsy is a chronic neurological disorder affecting sleep-wake regulation¹
- It is characterized by excessive daytime sleepiness (EDS), abnormal REM sleep phenomena including cataplexy, sleep-related hallucinations, sleep paralysis, and disrupted nocturnal sleep^{1,2}
- Type 1 narcolepsy is Narcolepsy with Cataplexy (emotionally induced muscle weakness)¹
- Additional features of narcolepsy include cognitive impairment such as lack of concentration, memory difficulties, and brain fog³
- Most patients with narcolepsy require pharmacotherapy, yet despite available options, most continue to experience symptoms which can be burdensome, impairing daily functioning, reducing productivity, and diminishing overall quality of life⁴

REM, rapid eye movement.

1. American Academy of Sleep Medicine. *ICSD-3-TR*. Chicago, IL: 2023. 2. España RA, Scammell TE.

Sleep. 2011;34(7):845-858. 3. Rosenberg R, et al. *J Clin Sleep Med*. 2024;20(4):643-651.

4. Krahn LE, et al. *Adv Ther*. 2022;39(1):221-243.



AXS-12 (reboxetine)

- AXS-12 (reboxetine) is a highly selective and potent norepinephrine reuptake inhibitor and cortical dopamine modulator¹
- AXS-12 regulates noradrenergic activity, which helps maintain muscle tone during wakefulness: it may modulate noradrenergic and dopaminergic pathways to stabilize sleep-wake states, enhance alertness, and improve cognition²
- It is approved in multiple countries outside the US for the treatment of major depressive disorder³

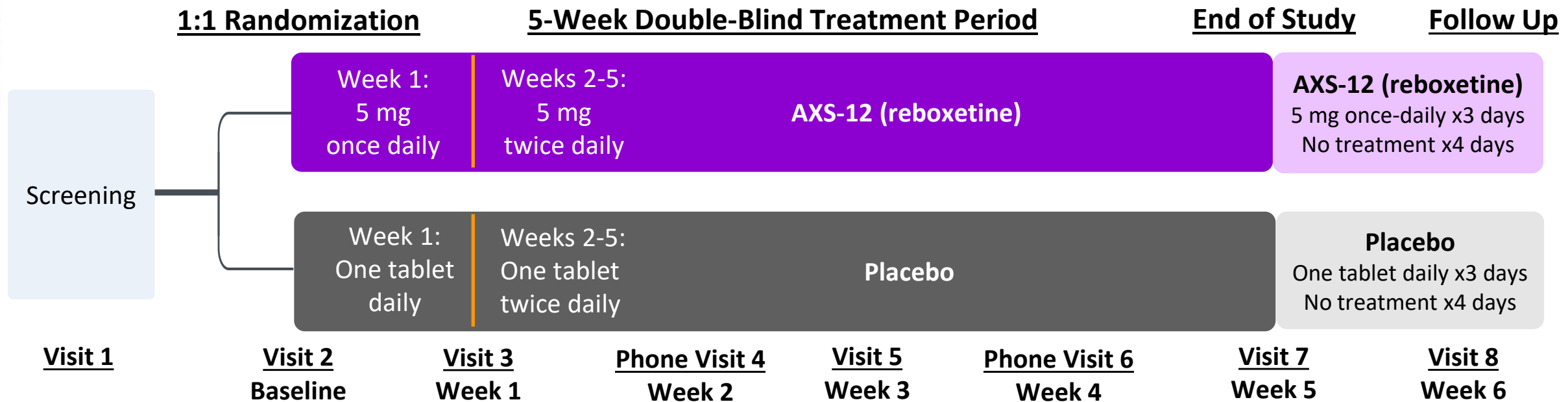
SYMPHONY Study Objective

To assess the efficacy and safety of AXS-12 compared to placebo for treating cataplexy in narcolepsy in the Phase 3 SYMPHONY Trial



SYMPHONY Trial Design

- Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in participants with a diagnosis of NT1
- Following screening, participants were randomized 1:1 to treatment with AXS-12 or placebo for 5 weeks



Eligibility Criteria

Key Inclusion Criteria

- Aged 15-75 years
- Diagnosis of NT1 with:
 - ≥ 7 cataplexy attacks/week, or
 - ≥ 14 across 2 weeks

Key Exclusion Criteria

- Diagnosis of another clinically significant condition potentially causing EDS

- Concurrent use of modafinil/armodafinil was allowed if dose was stable for ≥ 3 weeks before treatment start and stable throughout trial
- Anticataleptics were withdrawn ≥ 7 days before start of treatment



Endpoints

Primary Endpoint

- Change from Baseline to Week 5 in the weekly frequency of cataplexy attacks

Select Secondary Endpoints

- Percentage of participants with:
 - Cataplexy remission
 - Cataplexy-free days
- Change in severity of EDS (CGI-S)
- Change in frequency of inadvertent naps or sleep attacks (NSAQ)
- Change in score on cognitive items of the FOSQ-10



Baseline Sociodemographic and Clinical Characteristics

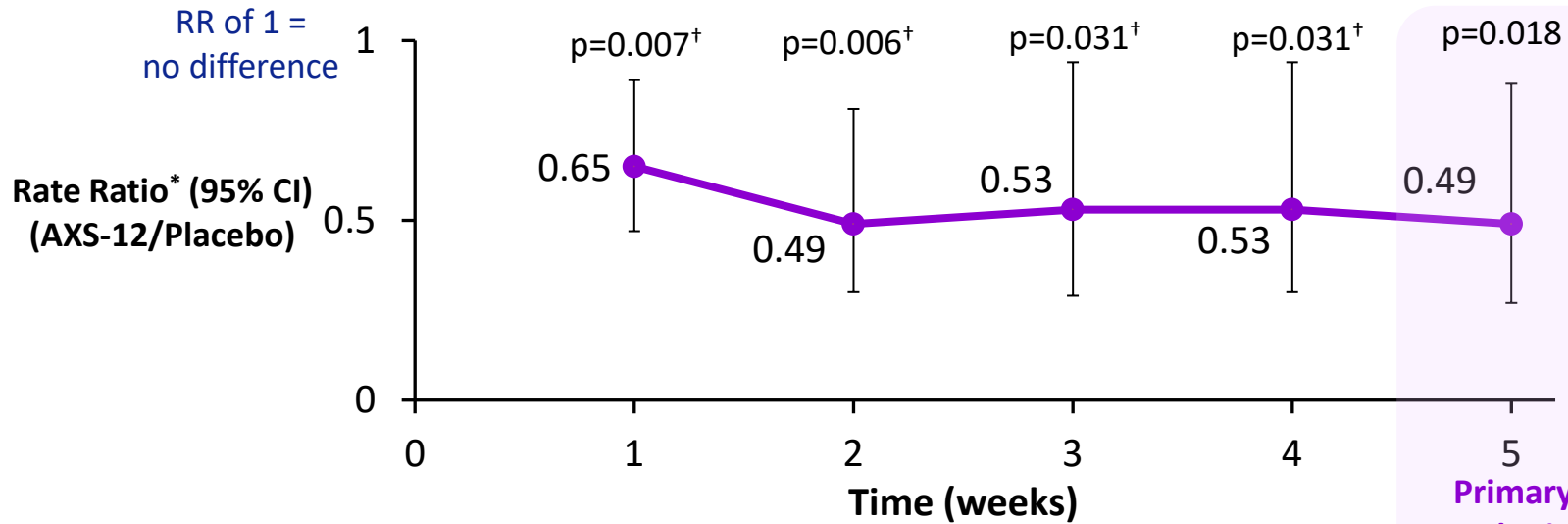
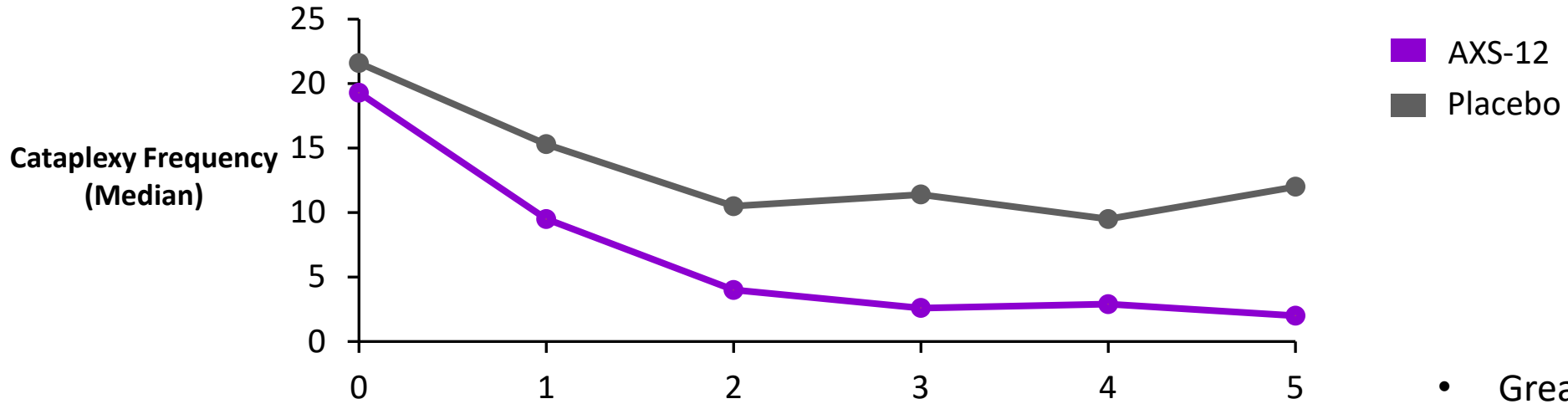
	AXS-12 (N=46)	Placebo (N=44)
Age, mean (SD), years	36.0 (13.4)	34.2 (12.1)
Sex, female, n (%)	25 (54.3)	29 (65.9)
Race, n (%)		
White	27 (58.7)	28 (63.6)
Black or African American	13 (28.3)	11 (25.0)
Asian	1 (2.2)	2 (4.5)
Other	2 (4.3)	1 (2.3)
BMI, mean (SD)	29.7 (6.3)	27.4 (5.6)
Time since diagnosis, 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

- The study population comprised 90 participants; baseline sociodemographic and clinical characteristics were similar across both treatment groups



Primary Endpoint:

AXS-12 Reduced Frequency of Cataplexy Attacks at Week 5



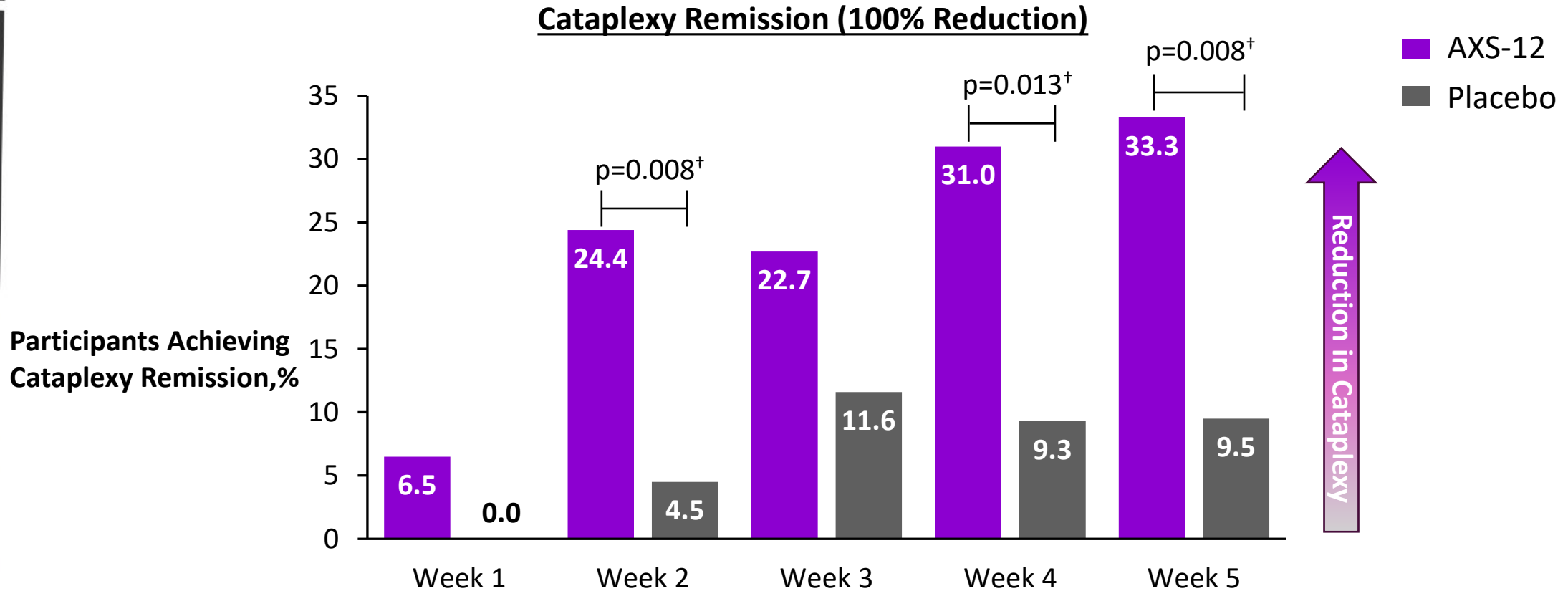
- Greater reductions in weekly cataplexy attacks with AXS-12 were observed as early as Week 1

[†]Nominal p-value.
RR, rate ratio

*Rate ratio compares the proportion of cataplexy attacks remaining at Week 5 (relative to Baseline) for AXS-12 vs. placebo

Secondary Endpoint:

AXS-12 Led to Higher Rates of Cataplexy Remission at Week 5



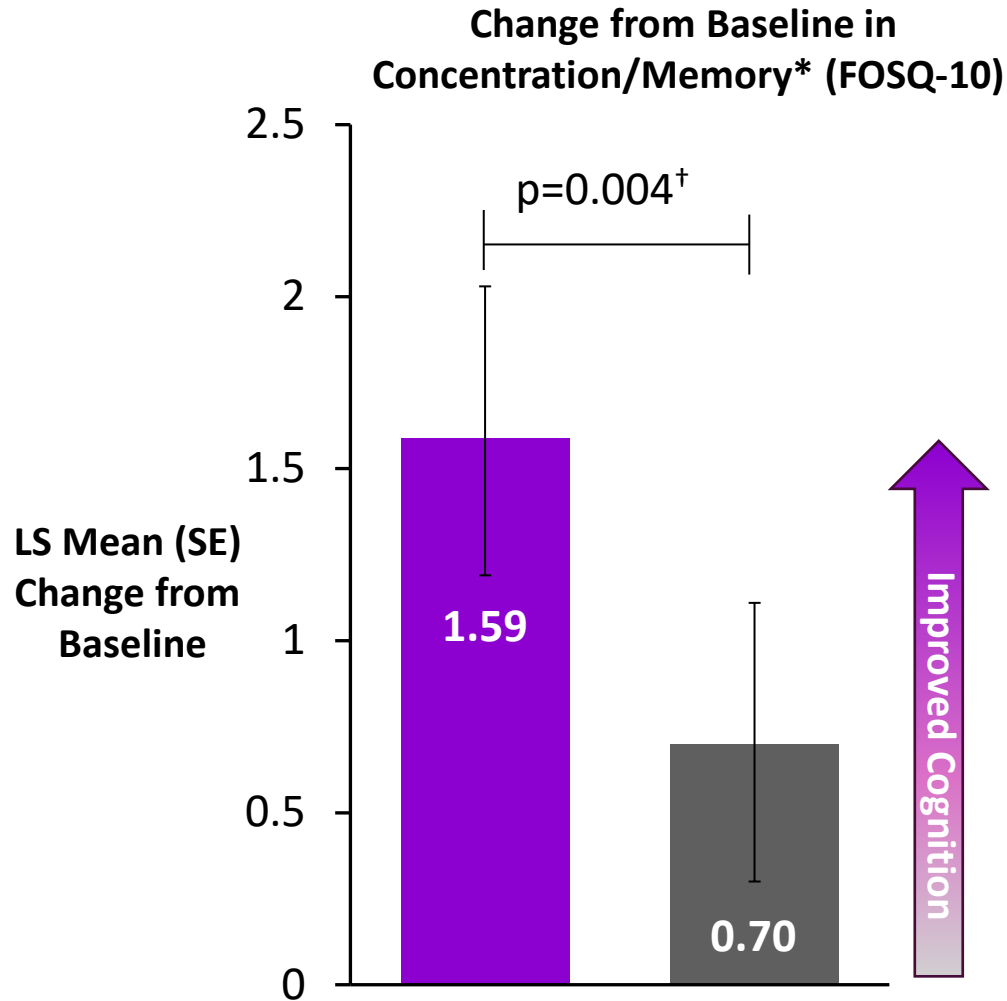
- Higher rates of cataplexy remission were observed with AXS-12 as early as Week 2
- Additionally, AXS-12 increased the percentage of cataplexy-free days per week relative to placebo (median 84.5% vs 22.6%; p=0.014[†])



[†]Nominal p-value.

Secondary Endpoints:

AXS-12 Improved Cognitive and Sleep Symptoms at Week 5

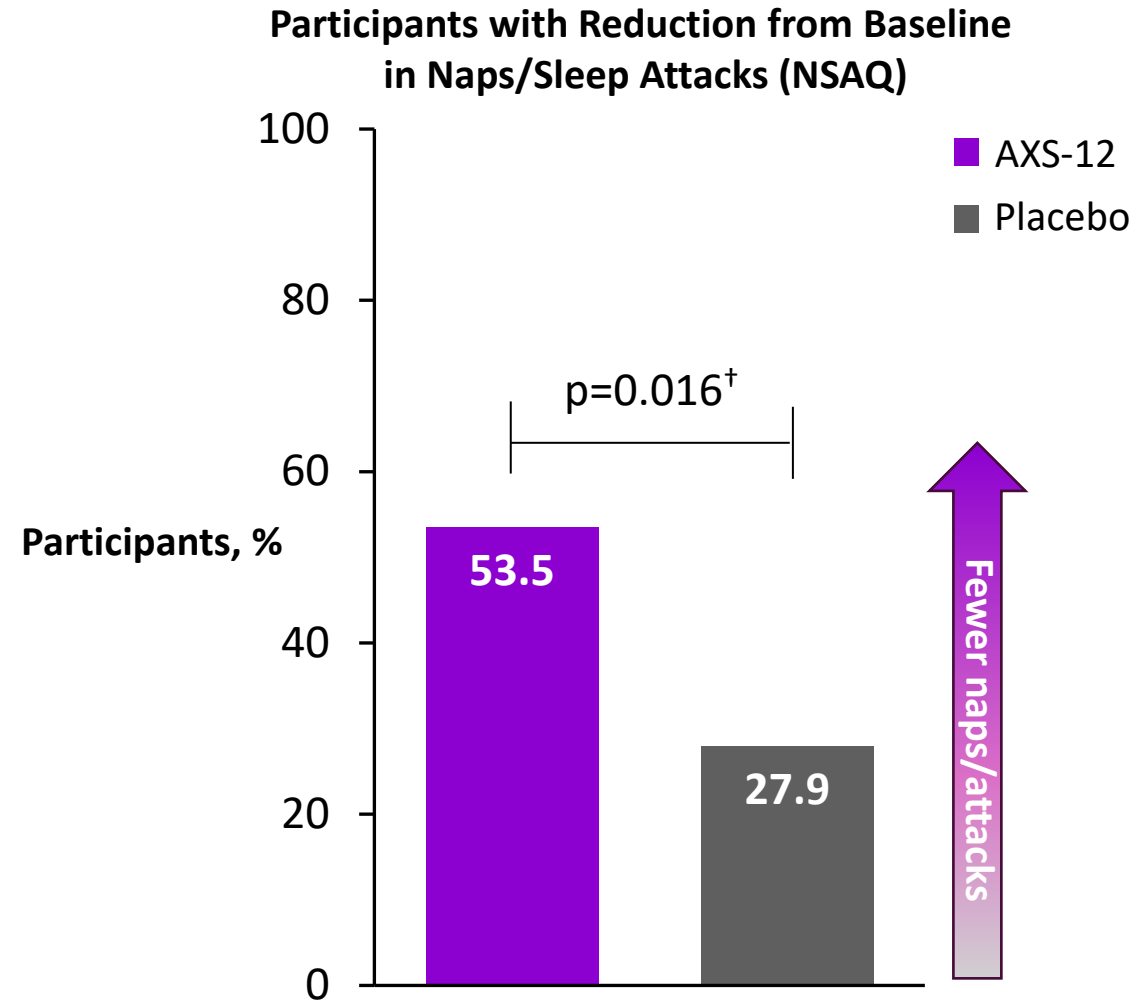


*Total score for 2 questions:

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?"

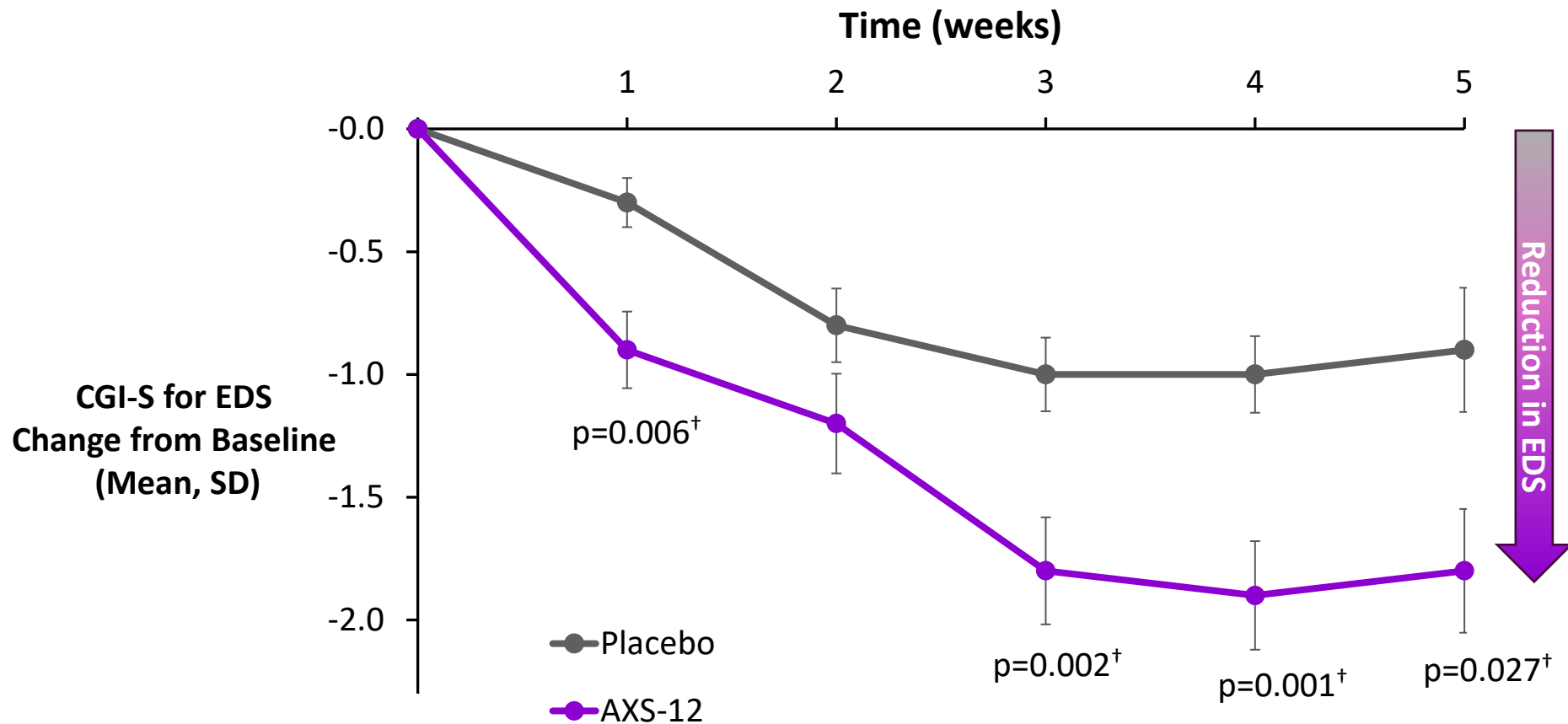
†Nominal p-value

FOSQ-10, Functional Items of Sleep Questionnaire-10; NSAQ, Narcolepsy Symptom Assessment Questionnaire.



Secondary Endpoint:

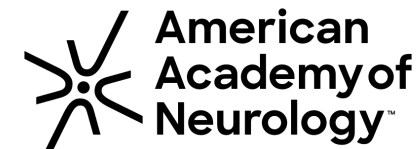
AXS-12 Reduced EDS Severity (CGI-S)



- Greater reductions in EDS were observed with AXS-12 compared to placebo as early as Week 1

[†]Nominal p-value

CGI-S, Clinical Global Impression Scale-Severity; EDS, excessive daytime sleepiness.



AXS-12 Safety and Tolerability Profile

Most Common TEAEs (≥ 5% of participants in AXS-12 arm)		
TEAE, n (%)	AXS-12	Placebo
Dry mouth	6 (13.0)	1 (2.3)
Nausea	6 (13.0)	0
Constipation	4 (8.7)	0
Paresthesia	4 (8.7)	0
Decreased appetite	3 (6.5)	0

- All commonly reported AEs 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 met its primary endpoint, significantly reducing weekly cataplexy attacks compared to placebo
- AXS-12 also reduced EDS and improved subjective cognitive function highlighting its potential to impact multiple symptoms of narcolepsy
- AXS-12 was generally well-tolerated and discontinuations due to adverse events were uncommon
- These results confirm and extend those from the Phase 2 CONCERT trial¹, which showed significant improvements in cataplexy, EDS, sleep quality and cognitive function
- These findings highlight the positive therapeutic impact of AXS-12 on persons with narcolepsy, who experience a substantial burden of disease²



EDS, excessive daytime sleepiness.

1. O’Gorman C, et al. Presented at APSS 2020. 2. Thorpy MJ, Hiller G. Am Health Drug Benefits. 2017 Jul;10(5):233-241

Disclosures & Acknowledgements

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.

CS serves as a consultant to Axsome Therapeutics.

AC, and **HT** are current employees of Axsome Therapeutics.

EBL is a former employee of Axsome Therapeutics.

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