

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

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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 cycle¹ AXS-12 (reboxetine) is a highly selective norepinephrine reuptake inhibitor under development for treatment of narcolepsy²
- 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 status³
- 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 period⁴
- 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

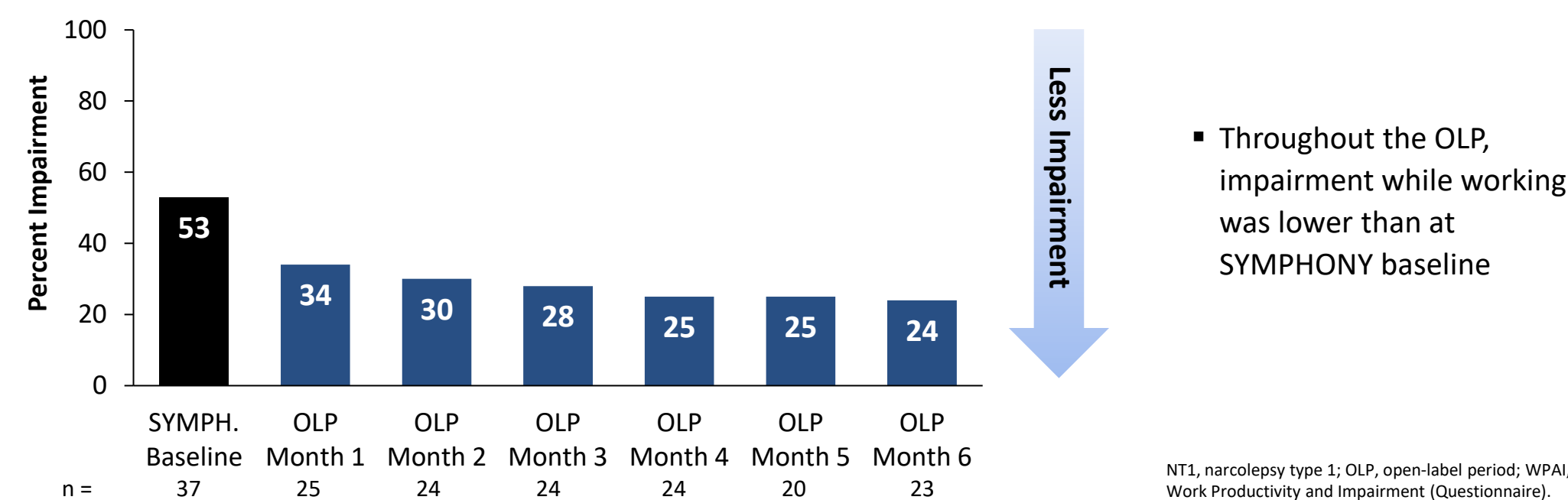
Table 1. Baseline Sociodemographic and Clinical Characteristics for ENCORE Participants	OLP (N=68)	DBRWP (N=42)
Age, years, mean (SD)	36.3 (13.2)	36.5 (13.1)
Sex, female, n (%)	41 (60)	26 (62)
Race, n (%)		
White	39 (57)	24 (57)
Black or African American	23 (34)	15 (36)
Asian	3 (4)	1 (2)
Other	2 (3)	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 DBRWP

^aBaseline 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.

Work Impairment

Figure 5. Impairment While Working Due to Narcolepsy: WPAI



References

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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 8-13; 2025; Seattle, WA, USA.

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QR Code

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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.

Excessive Daytime Sleepiness

Figure 1. Change in EDS: PGI-C

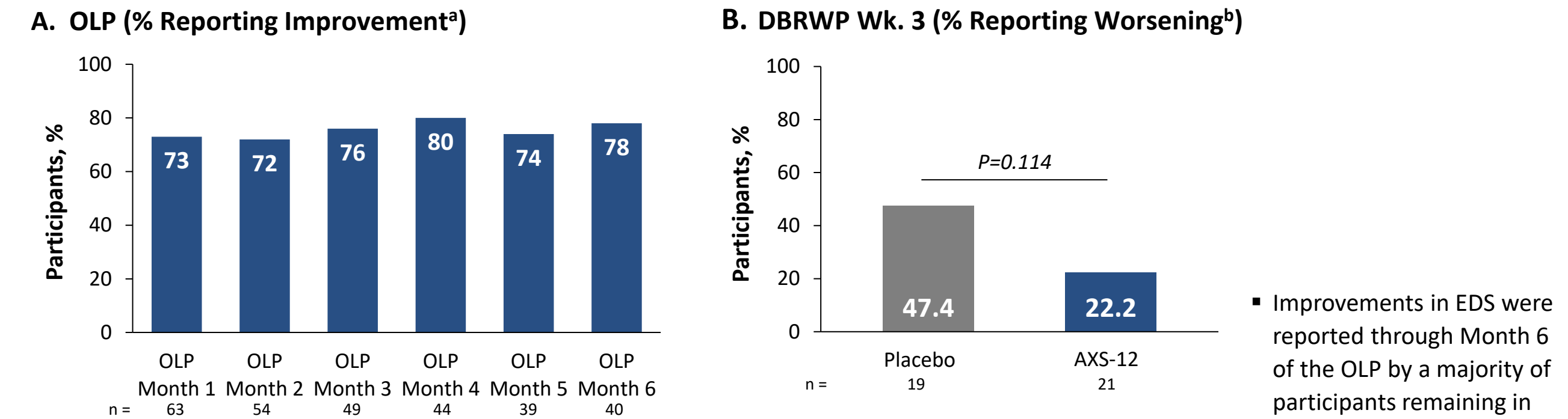
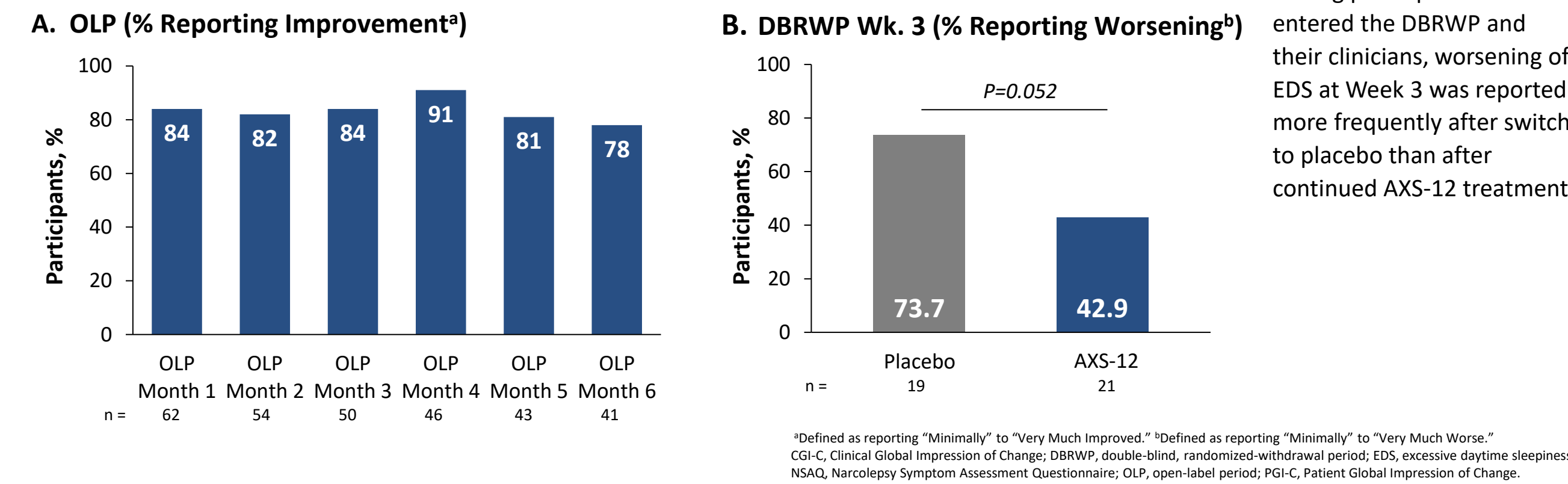


Figure 2. Change in EDS: CGI-C



Concentration

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

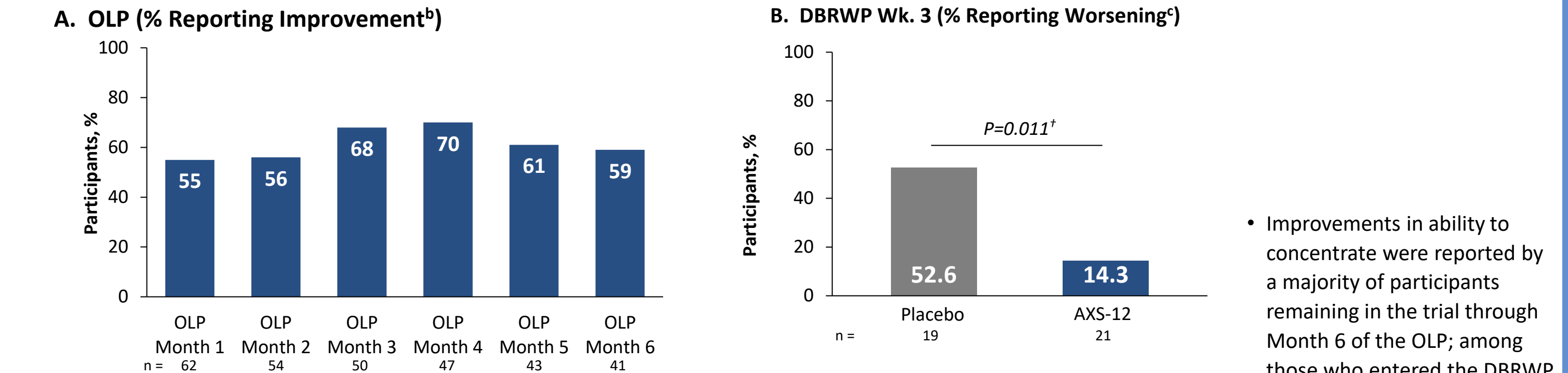
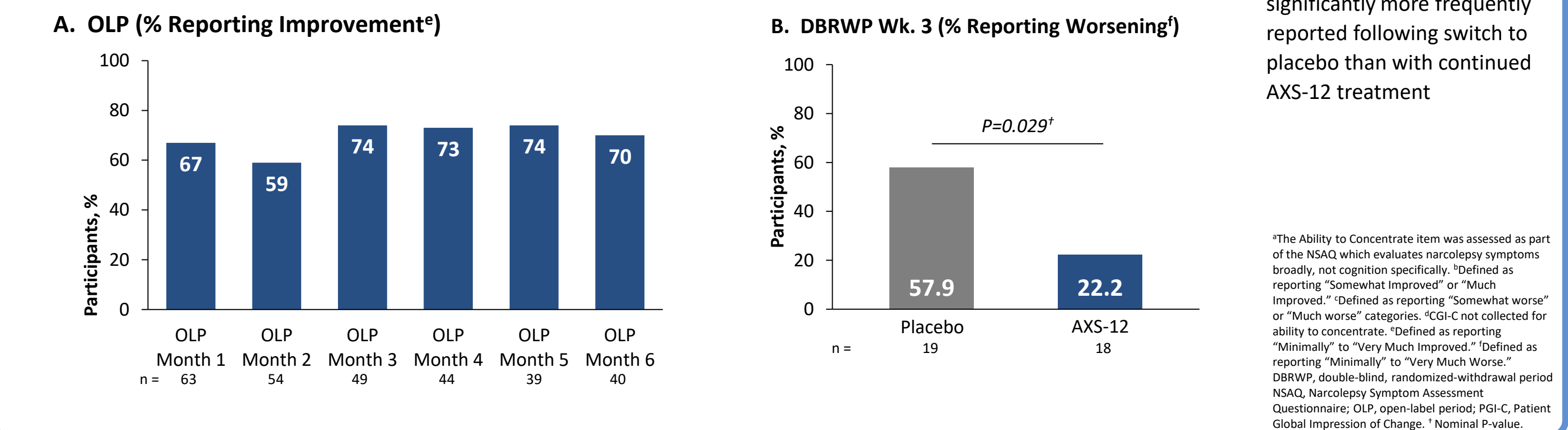


Figure 4. Change in Ability to Concentrate: PGI-C^d



Overall Narcolepsy Status

Figure 6. Change in Narcolepsy Status: PGI-C

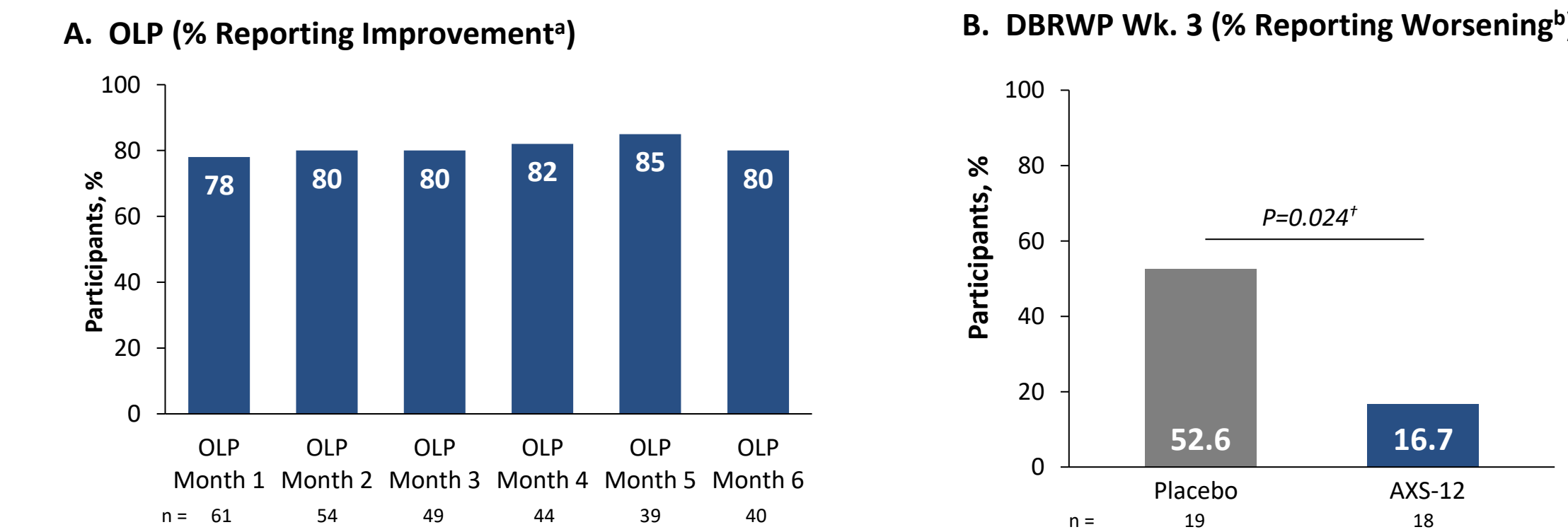
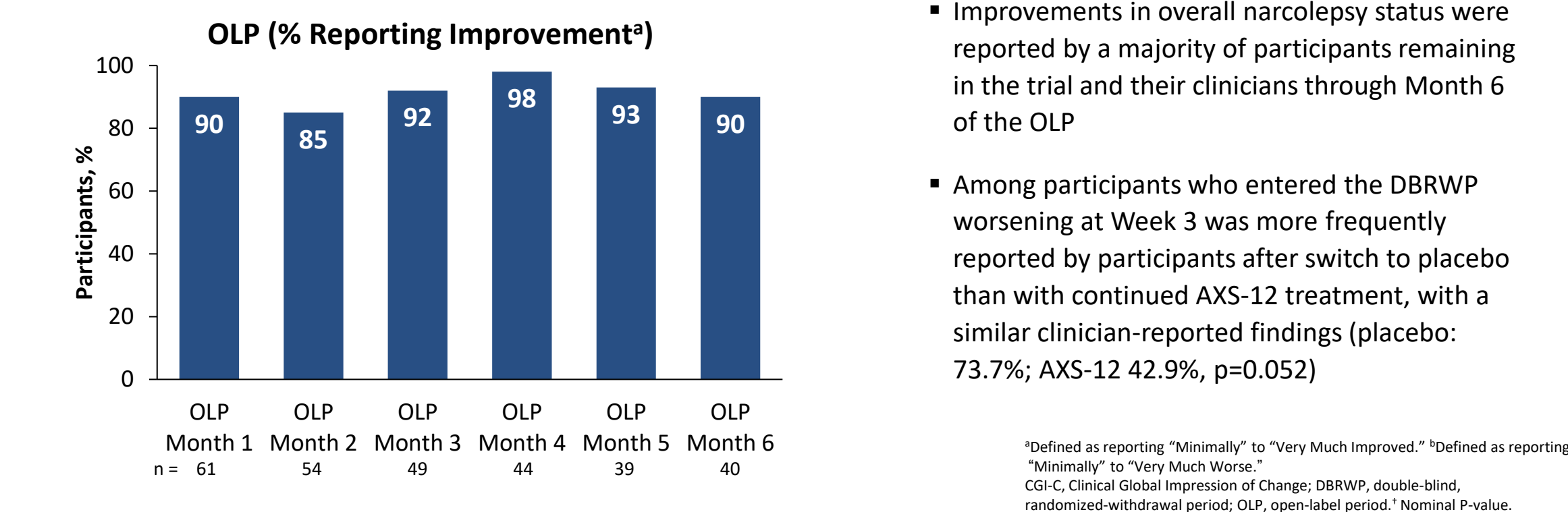


Figure 7. Change in Narcolepsy Status Assessed by CGI-C



Safety and Tolerability^a

Table 2. Treatment-emergent Adverse Events (TEAEs)	OLP (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

^aOLP 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
^bOne participant had increased alanine aminotransferase and one participant had increased liver function test on the day of randomization while withdrawing 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