
# Impact of AXS-12 on Symptom Severity and Functional Impairment in Narcolepsy: Results from the Phase 3 SYMPHONY Trial

**Michael J. Thorpy**, Lois E. Krahn, Richard K. Bogan, Bruce C. Corser, Colin Shapiro, Dan Chen, Angad Chhabra, Eileen B. Leary, Herriot Tabuteau

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# Learning Objectives

*Upon completion of this activity, participants should be able to:*

- Evaluate the effect of AXS-12 (reboxetine) on symptom severity, daily functioning, and mood in the Phase 3 SYMPHONY trial of AXS-12 in narcolepsy

# Introduction

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- Narcolepsy is a chronic neurologic condition associated with severe symptom burden, impaired functioning, and reduced quality of life[1]
  - Comorbid mood disorders, such as anxiety and depression, are also common and can further impact daily life[2]

- Most patients require pharmacotherapy, yet despite available options, often continue to experience burdensome symptoms which impair daily functioning, reduce productivity, and diminish quality of life[2]

**1.** Tadrous R, et al. *J Sleep Res.* 2021;30(6):e13383. **2.** Krahn LE, et al. *Adv Ther.* 2022;39(1):221-243.

# AXS-12 (reboxetine)

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- AXS-12 (reboxetine) is a selective norepinephrine reuptake inhibitor and cortical dopamine modulator[3] under investigation for the treatment of narcolepsy

- In the Phase 3 SYMPHONY trial, AXS-12 met the primary endpoint, a statistically significant reduction in weekly cataplexy attacks from baseline to Week 5 versus placebo[1]
  - Additionally, AXS-12 improved both EDS and subjective cognitive function

- Here, we report secondary endpoints assessing symptom severity, daily functioning, and mood

**1.** Thorpy H, et al. Presented at ESRS 2024.

# Methods-Study Design

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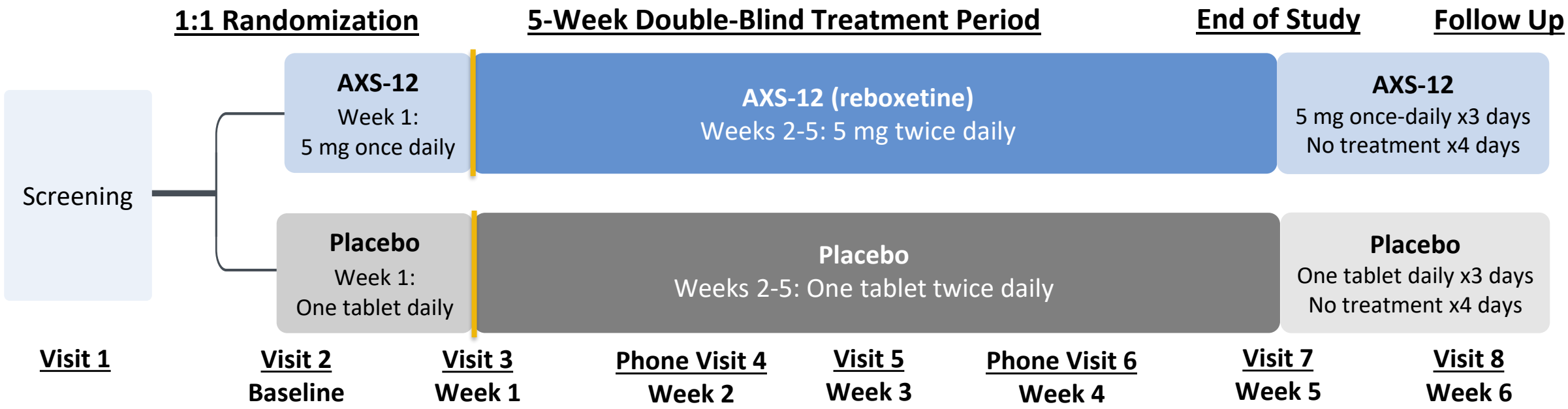
- Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in participants with a diagnosis of NT1
- Following screening, participants were randomized 1:1 to treatment with AXS-12 or placebo for 5 weeks




NT1, narcolepsy type 1.

# Methods-Eligibility Criteria

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## 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

EDS, excessive daytime sleepiness; NT1, narcolepsy type 1.

# Methods-Endpoints

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## Select Secondary Endpoints

The effect of AXS-12 compared to placebo was evaluated on each of the following outcomes at Week 5:

- **Clinical Global Impression of Change-Severity (CGI-S) for Narcolepsy Overall:** Clinician-rated measure of overall symptom severity
  - Scored from 1 (normal) to 7 (severely ill)

- **Functional Outcomes of Sleep (FOSQ)-10:** Patient-reported measure of the impact of excessive daytime sleepiness on daily functioning across five subscales, scored from 1 (extreme difficulty) to 4 (no difficulty)
  - Total scores range from 5 to 20, with higher scores indicating better functioning

- **EuroQoL 5-Dimension 5-Level (EQ-5D-5L):** Patient-reported assessment of health-related quality of life across five domains, each scored from 1 (no problems) to 5 (extreme problems)
  - Only results of the Anxiety/Depression domain are reported
  - **Anxiety/depression domain:** (1 = no anxiety/depression, 5 = extreme anxiety/depression)

# Baseline Characteristics Were Balanced Between Treatments

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| 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 |
| **Epworth Sleepiness Scale score, mean (SD)** | 18.3 (3.1) | 17.3 (3.3) |
| **CGI-S for Narcolepsy Overall** | 5.2 (1.0) | 4.9 (1.0) |
| **EQ-5D-5L, ≥ slightly anxious/depressed, %** | 47.8 | 45.5 |
| **FOSQ-10, mean (SD)** | 11.1 (3.1) | 11.6 (3.2) |
| **Use of modafinil or armodafinil, %** | 32.6 | 29.5 |

BMI, body mass index; CGI-S, Clinical Global Impression of Severity; EDS, excessive daytime sleepiness; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FOSQ-10, Functional Items of Sleep Questionnaire-10.

# Greater Improvement in Overall Narcolepsy Severity With AXS-12 (CGI-S)

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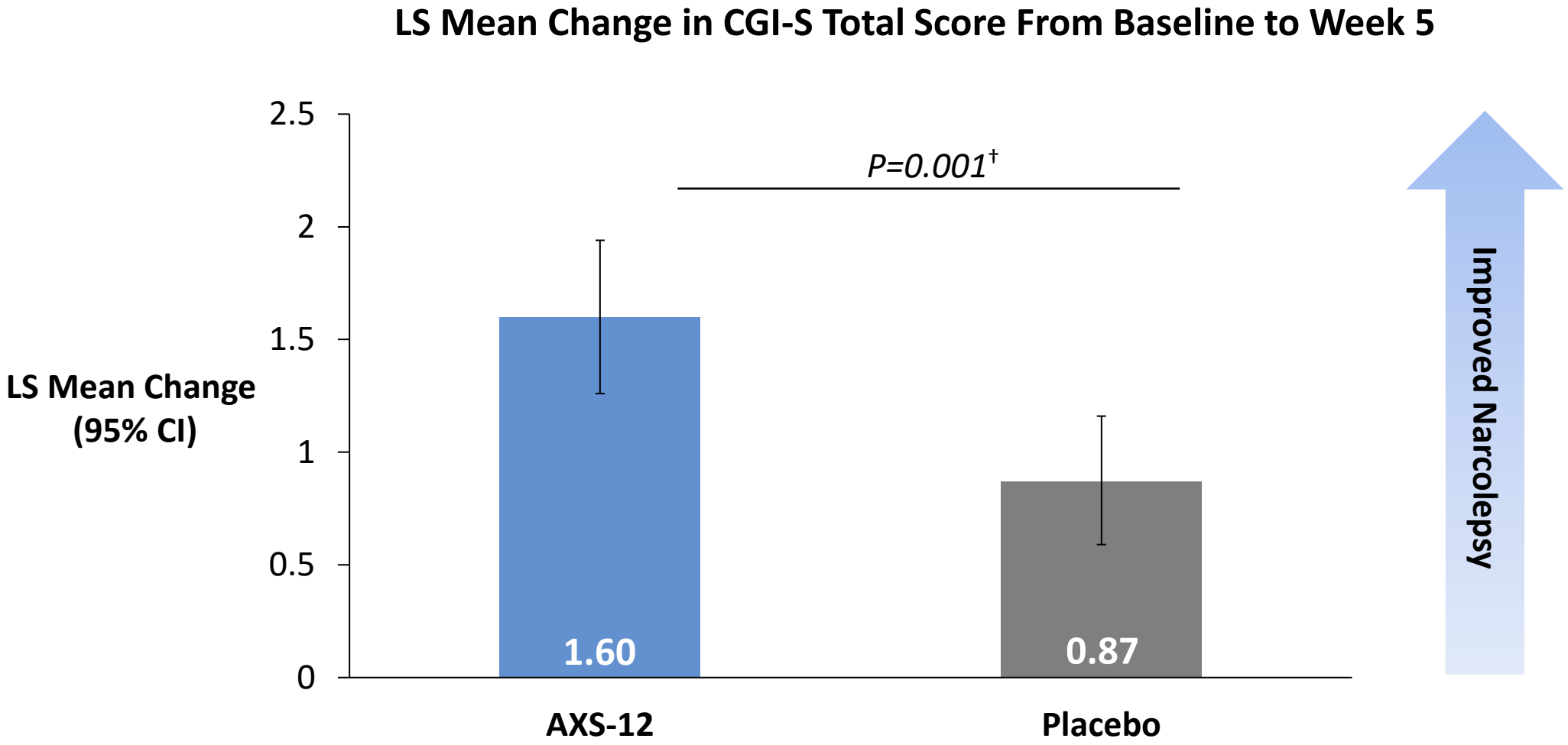


CGI-S, Clinical Global Impression of Severity; LS, least squares.
†Nominal p-value.

# More Participants Achieved Improvement in Anxiety/Depression With AXS-12 (EQ-5D-5L)

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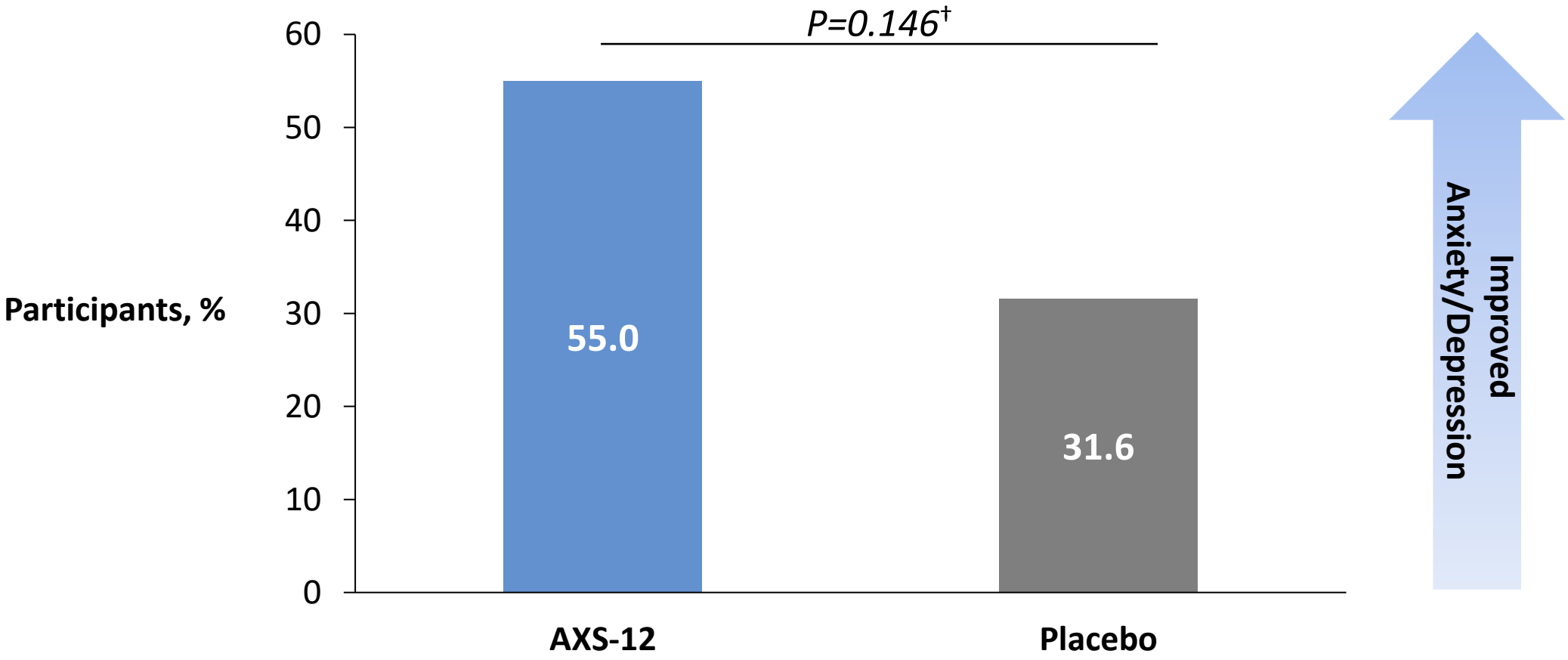
**Participants Achieving Improvement in Anxiety/Depression Domain From Baseline to Week 5**




EQ-5D-5L, EuroQol 5-Dimension, 5-Level.
†Nominal p-value. *Improvement defined as a >=1-level reduction from baseline to Week 5.

# Greater Improvement in Function and Quality of Life With AXS-12 (FOSQ-10)

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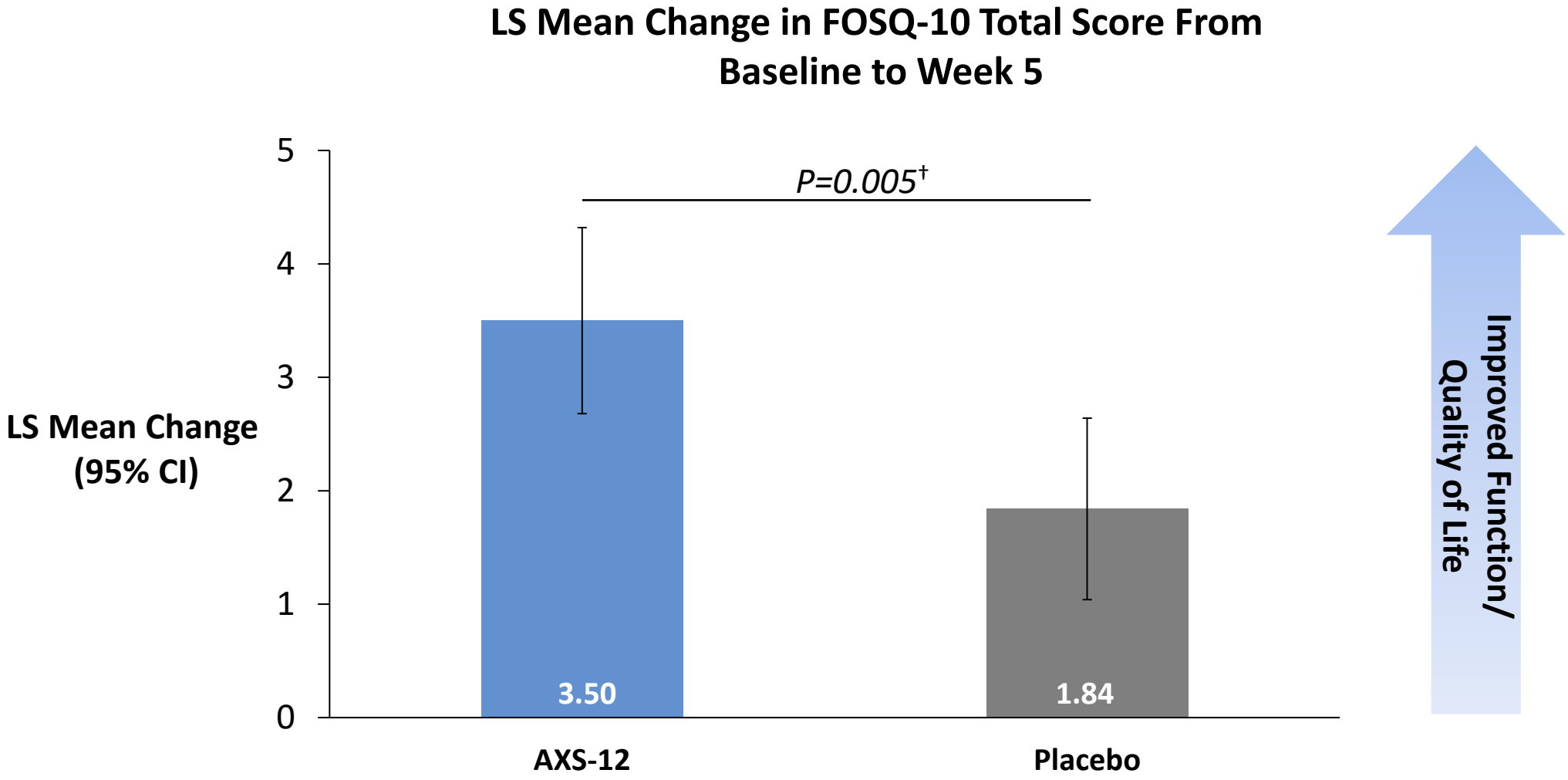


FOSQ-10, Functional Items of Sleep Questionnaire-10; LS, least squares.
†Nominal p-value.

# Greater Improvement Across FOSQ-10 Subdomains With AXS-12

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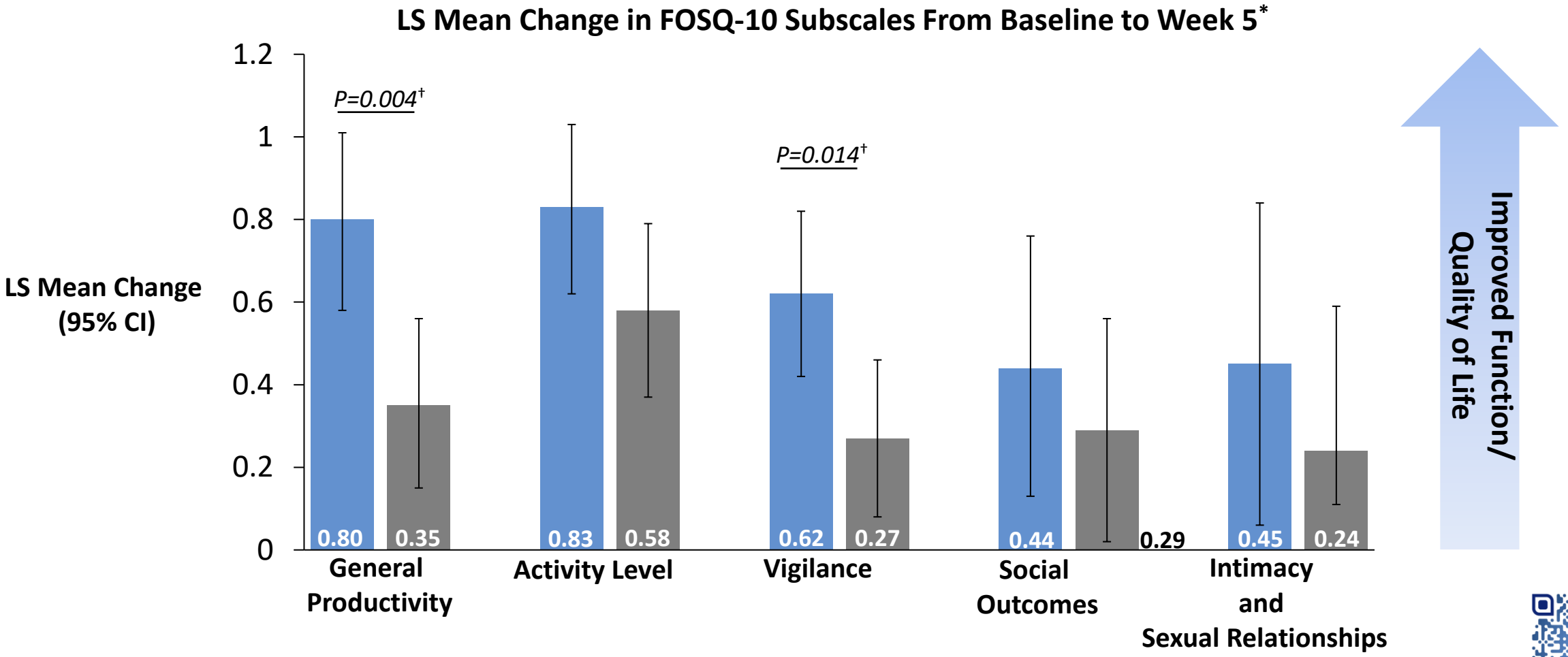


FOSQ-10, Functional Items of Sleep Questionnaire-10; LS, least squares.
*Baseline values of subscales were balanced between arms. †Nominal p-value.

# AXS-12 Safety and Tolerability Profile

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| 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

AE, adverse event; TEAE, treatment-emergent adverse event.

# Conclusions

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- AXS-12 demonstrated a reduction in the clinical impression of overall narcolepsy symptom severity compared to placebo
- AXS-12 improved mood-related symptoms, with more participants reporting reduced anxiety/depression than with placebo
- AXS-12 improved daily functioning impaired by excessive daytime sleepiness, particularly in productivity and vigilance domains, and with numerical superiority to placebo across all other domains
- Combined with prior findings on cataplexy and cognitive function, as well as favorable safety/tolerability, these results support the potential of AXS-12 as a therapeutic option addressing multiple burdensome symptoms of narcolepsy

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**M. Thorpy** serves as a consultant to Axsome Therapeutics.

**L. Krahn** serves as a consultant to Axsome Therapeutics.

**R. 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.

**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, Inc.

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

**E. B. Leary** is a former employee of Axsome Therapeutics, Inc.

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