



SLEEP 2025

Seattle, WA / June 8 – 11

A JOINT MEETING

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

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Introduction

- Narcolepsy is a chronic neurologic condition associated with severe symptom burden, impaired functioning, and reduced quality of life¹
 - Comorbid mood disorders, such as anxiety and depression, are also common and can further impact daily life²
- Most patients require pharmacotherapy, yet despite available options, often continue to experience burdensome symptoms which impair daily functioning, reduce productivity, and diminish quality of life²



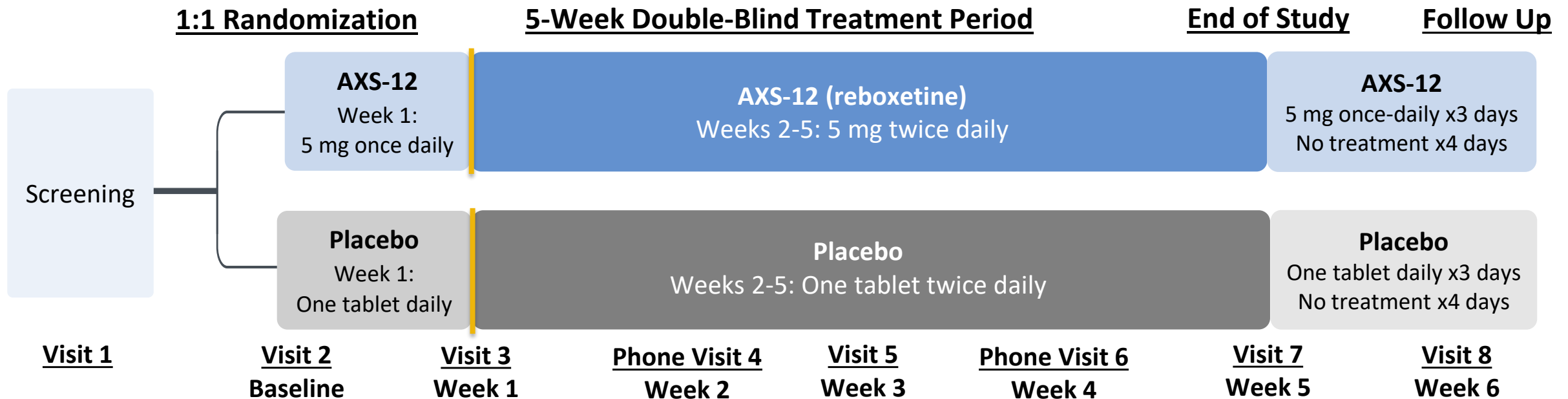
AXS-12 (reboxetine)

- AXS-12 (reboxetine) is a selective norepinephrine reuptake inhibitor and cortical dopamine modulator¹ 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 placebo²
 - Additionally, AXS-12 improved both EDS and subjective cognitive function
- Here, we report secondary endpoints assessing symptom severity, daily functioning, and mood



Methods-Study 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



Methods-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- Anticataleptics were withdrawn ≥ 7 days before start of treatment



Methods-Endpoints

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 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

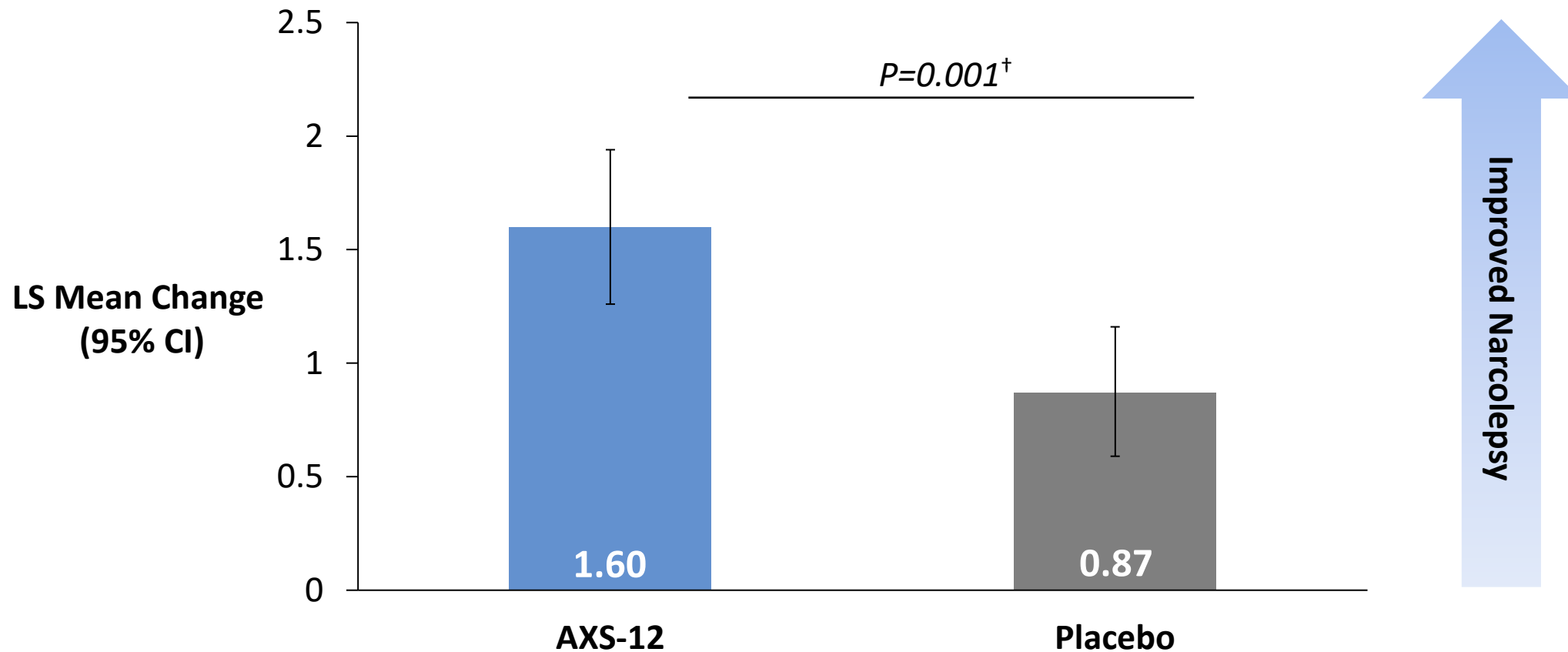
Baseline Sociodemographic and Clinical Characteristics		
	AXS-12 (N=46)	Placebo (N=44)
Age, mean (SD), years	36.0 (13.4)	34.2 (12.1)
Sex, female, n (%)	25 (54.3)	29 (65.9)
Race, n (%)		
White	27 (58.7)	28 (63.6)
Black or African American	13 (28.3)	11 (25.0)
Asian	1 (2.2)	2 (4.5)
Other	2 (4.3)	1 (2.3)
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, \geq 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



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

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LS Mean Change in CGI-S Total Score From Baseline to Week 5



CGI-S, Clinical Global Impression of Severity; LS, least squares.

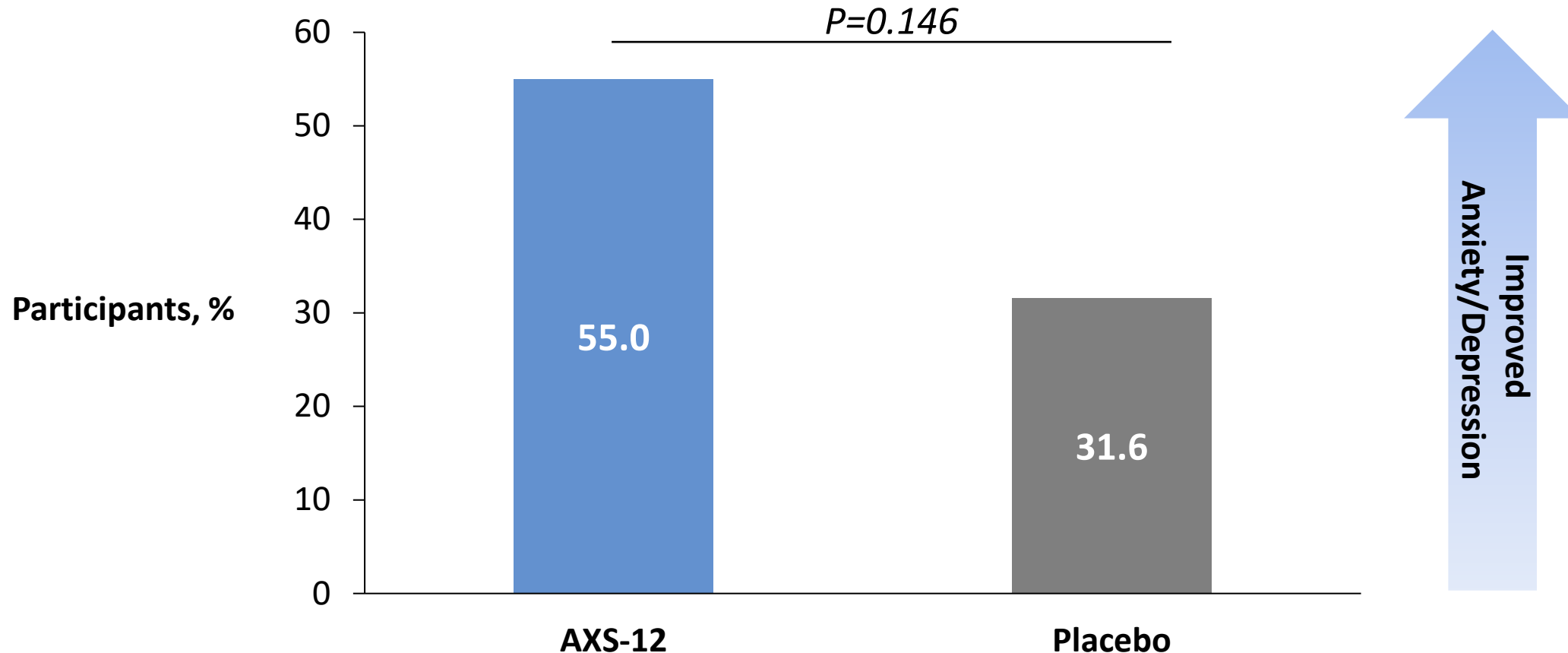
[†]Nominal p-value.



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.

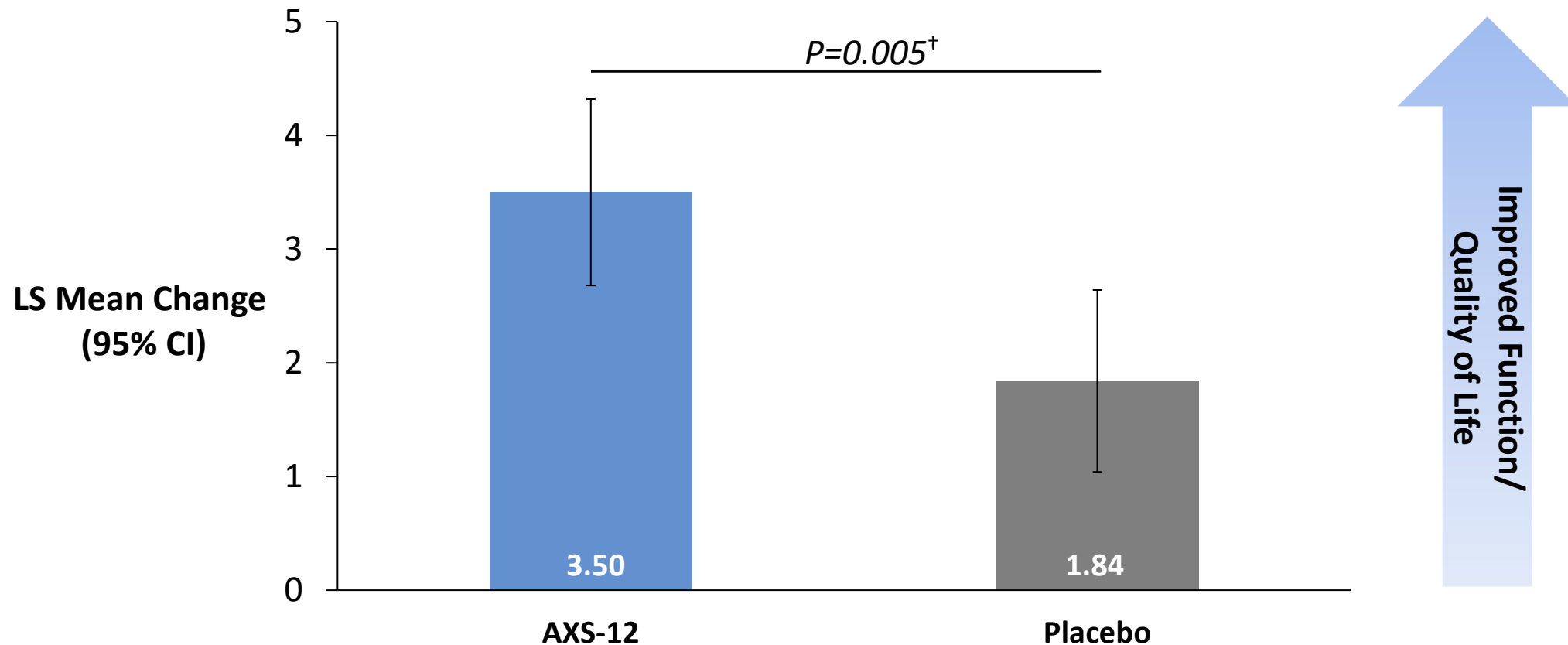
*Improvement defined as a ≥ 1 -level reduction from baseline to Week 5.



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

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LS Mean Change in FOSQ-10 Total Score From
Baseline to Week 5



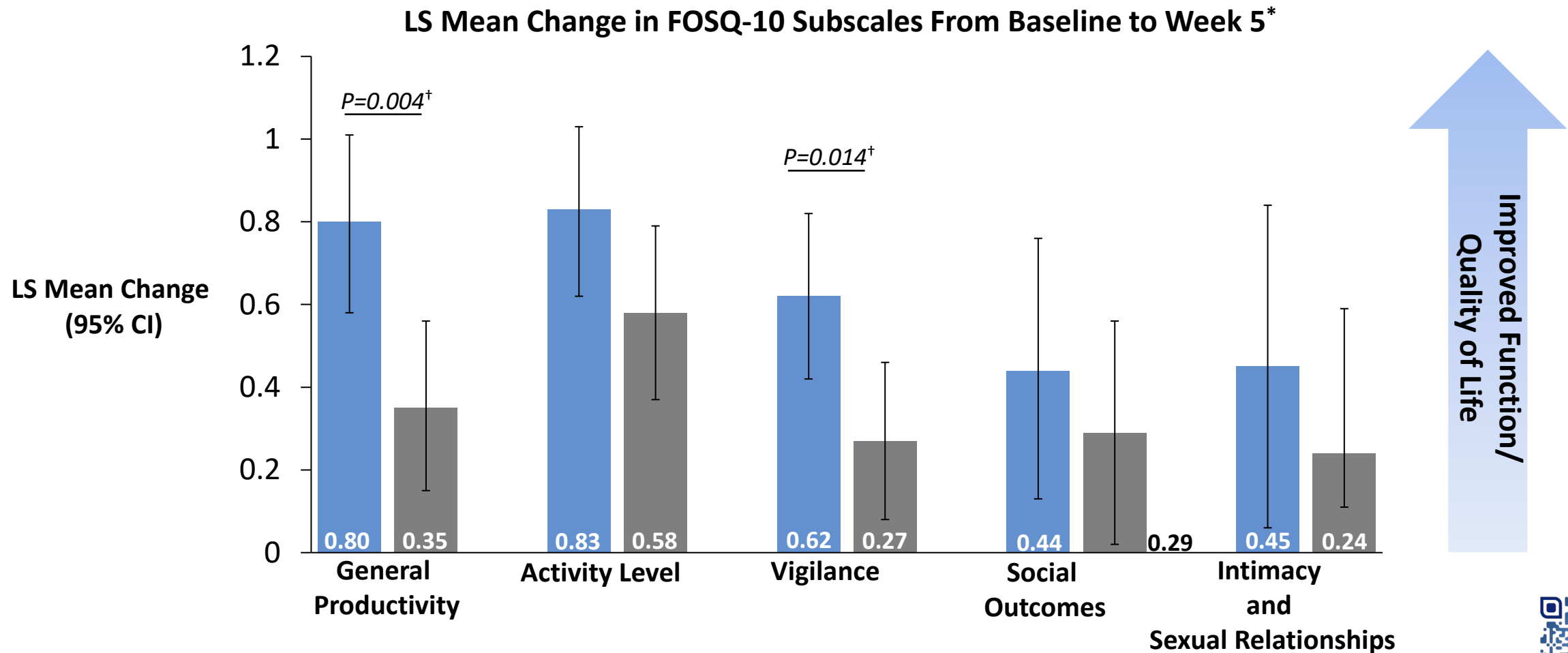
FOSQ-10, Functional Items of Sleep Questionnaire-10; LS, least squares.

[†]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

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 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



Acknowledgements and Disclosures

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, provided medical writing and editorial support, which was funded by Axsome Therapeutics.

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