NASDAQ: AXSM

AXSOME THERAPEUTICS

CONCERT Phase 2 Trial of AXS-12 in Narcolepsy

Topline Results

Conference Call

December 3, 2019

AXS-12 in Narcolepsy
CONCERT Phase 2 Trial Topline Results

Introduction	**Mark Jacobson**, Senior Vice President, Operations
Overview and Summary	**Herriot Tabuteau, MD**, Chief Executive Officer
CONCERT Trial Design & Results	**Cedric O'Gorman, MD**, Senior Vice President, Clinical Development & Medical Affairs
Q&A	**Presenters, Nick Pizzie**, Chief Financial Officer and **Dave Marek,** Chief Commercial Officer
Concluding Remarks	**Herriot Tabuteau, MD**, Chief Executive Officer

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Overview and Summary

Herriot Tabuteau, MD

AXSOME THERAPEUTICS

Chief Executive Officer
Axsome Therapeutics, Inc.

AXS-12: CONCERT Phase 2 Trial in Narcolepsy
Summary of Topline Results

- AXS-12 (reboxetine) met the prespecified primary endpoint resulting in a highly statistically significantly reduction in the number of cataplexy attacks as compared to placebo
- AXS-12 also significantly reduced excessive daytime sleepiness, assessed by the Epworth Sleepiness Scale and by the frequency of inadvertent naps or sleep attacks, as compared to placebo
- AXS-12 also resulted in statistically significant improvements in cognitive function, sleep quality and sleep-related symptoms
- The beneficial effects of AXS-12 were rapid being observed as early a Week 1
- AXS-12 was safe and well-tolerated with no reported serious adverse events (SAEs) and no discontinuations due to adverse events.
- Data support initiation of Phase 3 trials for AXS-12 in narcolepsy, anticipated in 2020

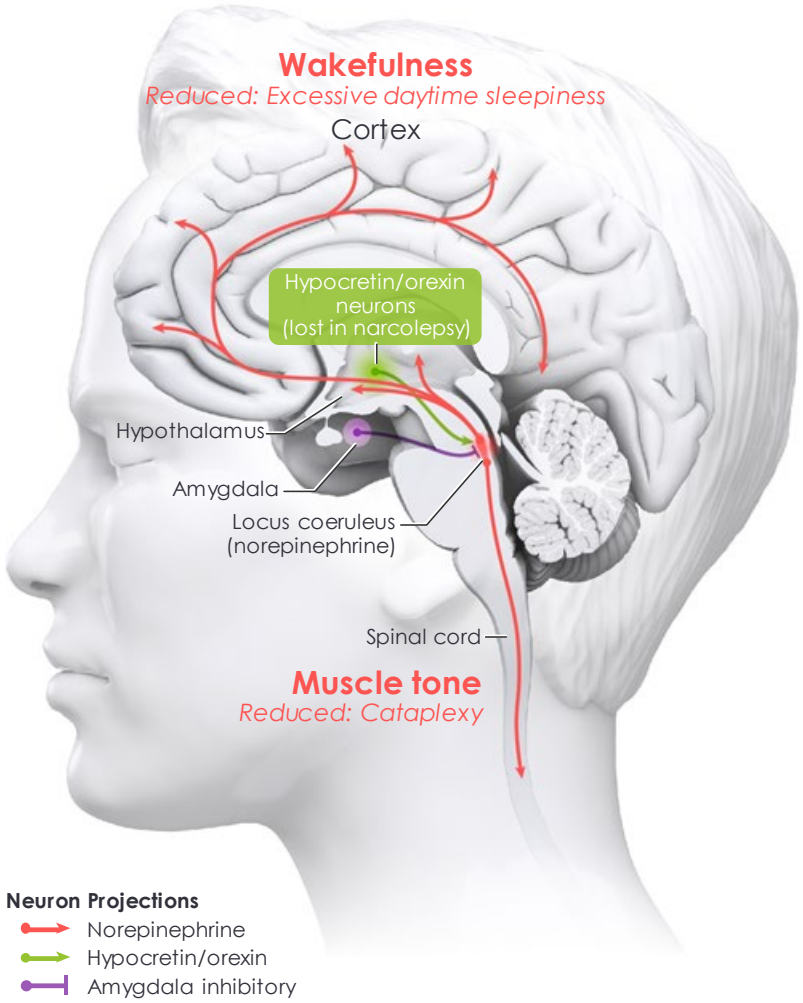
Narcolepsy: Overview

- Narcolepsy is a chronic, debilitating, neurologic condition characterized by:
  - Excessive daytime sleepiness (EDS)
  - Cataplexy: a sudden reduction or loss of muscle tone triggered by strong emotions
  - Disturbed nocturnal sleep
  - Sleep paralysis
  - Hypnagogic hallucinations
- Orphan condition: nearly 200K patients, with 50% diagnosed, and 25% treated
- Existing treatment options are limited, do not address all symptoms, provide variable efficacy, have significant side effects, and are mostly controlled substances
  - Only 1 agent currently approved to treat both cataplexy and EDS
- Urgent need for new treatments for patients that address the limitations of current agents

American Academy of Sleep Medicine. ICSD-2. Chicago, IL: 2005.
National Institute of Neurological Disorders and Stroke. 2011. http://www.ninds.nih.gov/disorders/narcolepsy/narcolepsy.htm. Accessed July 15, 2013.
España RA, Scammell TE. *Sleep*. 2011;34(7):845-858.

Narcolepsy:
Wakefulness and Cataplexy Mechanisms

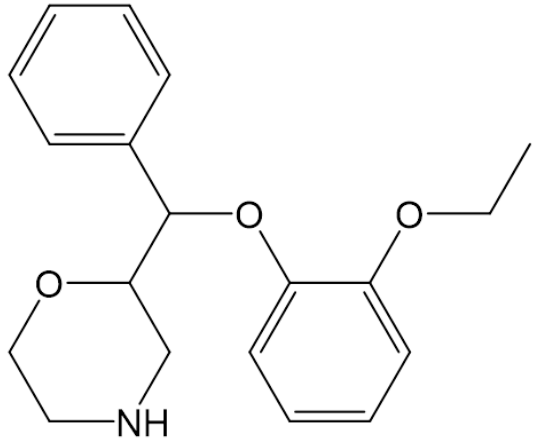
- Narcolepsy is caused by a loss of hypocretin neurons in the brain
- Hypocretin neurons normally excite norepinephrine neurons which promote wakefulness and help maintain muscle tone
- Hypocretin loss leads to dysregulation of norepinephrine neurons resulting in:
  - Decreased wakefulness during the day (EDS)
  - Loss of muscle tone while awake (cataplexy)
- AXS-12 improves regulation of norepinephrine signaling in narcolepsy



Szabo ST, et al. *Sleep Medicine Reviews* 43 (2019) 23-36

Narcolepsy:
AXS-12 (reboxetine) Overview

- AXS-12 (reboxetine) is a potent, highly selective norepinephrine reuptake inhibitor
- Rationale for development in narcolepsy:
  - Norepinephrine signaling is dysregulated in narcolepsy contributing to key symptoms
  - AXS-12 improves regulation of norepinephrine signaling
- AXS-12 is orally administered, dosed during the day, and has a well-characterized safety and tolerability profile
  - Not expected to be scheduled
- AXS-12 has been granted U.S. FDA Orphan Drug designation for the treatment of narcolepsy



CONCERT Trial Design & Results

Cedric O'Gorman MD, MBA

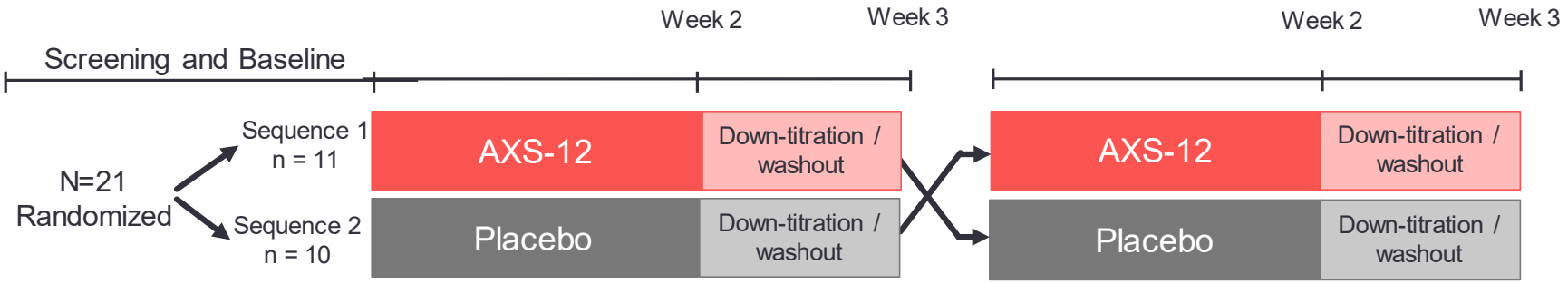
AXSOME THERAPEUTICS

Senior Vice President, Clinical Development and Medical Affairs
Axsome Therapeutics, Inc.

CONCERT: Study Design

CONCERT STUDY

Multi-center, Randomized, Double-blind, Placebo-controlled, 3-Week Crossover Study to Assess the Efficacy and Safety of AXS-12 for Cataplexy and Excessive Daytime Sleepiness in Subjects with Narcolepsy



- **Dose**
  - Week 1 – orally twice daily, total daily dose of 8 mg
  - Week 2 – orally twice daily, total daily dose of 10 mg
- **Key Inclusion Criteria**:
  - Adults with diagnosis of narcolepsy exhibiting cataplexy and excessive daytime sleepiness (EDS)
  - Male or female 18 – 70 years old
  - ESS Score > 10 at screening and baseline
  - At least 7 cataplexy attacks per week during screening

CONCERT:
Study Endpoints

CONCERT STUDY

Multi-center, Randomized, Double-blind, Placebo-controlled, 3-Week Crossover Study to Assess the Efficacy and Safety of AXS-12 for Cataplexy and Excessive Daytime Sleepiness in Subjects with Narcolepsy

- **Primary Endpoint:**
  - Change in the mean weekly number of cataplexy attacks, averaged over the 2-week treatment period (overall treatment effect)

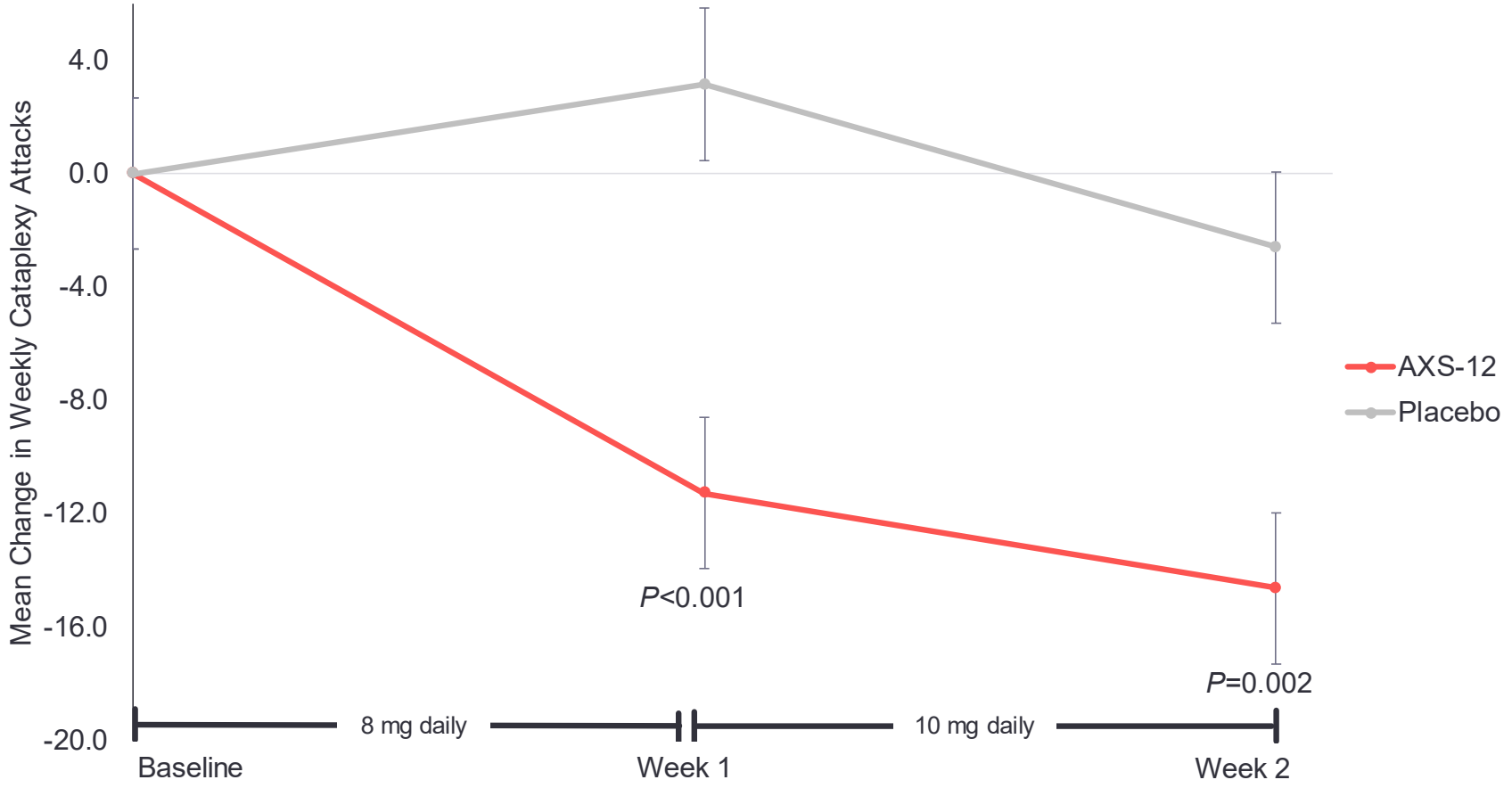
- **Secondary Efficacy Endpoints**:
  - Daytime sleepiness, measured by the Epworth Sleepiness Scale (ESS) and number of inadvertent naps
  - Cognitive function assessed using the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire (NSAQ)
  - Sleep quality and sleep-related symptoms (incl. nighttime awakenings, sleep paralysis, and hypnagogic hallucinations items of the NSAQ)

CONCERT:
Demographics and Baseline Characteristics

- Mean age (years): 32.6
- Mean time since diagnosis (years): 3.8
- Mean cataplexy attacks at baseline: 30.0 weekly attacks
- Mean Epworth Sleepiness Scale (ESS) score at baseline: 18.1
- Ability to Concentrate at baseline: rated “very poor”, “poor”, or “average” by all patients

Improved Cataplexy:

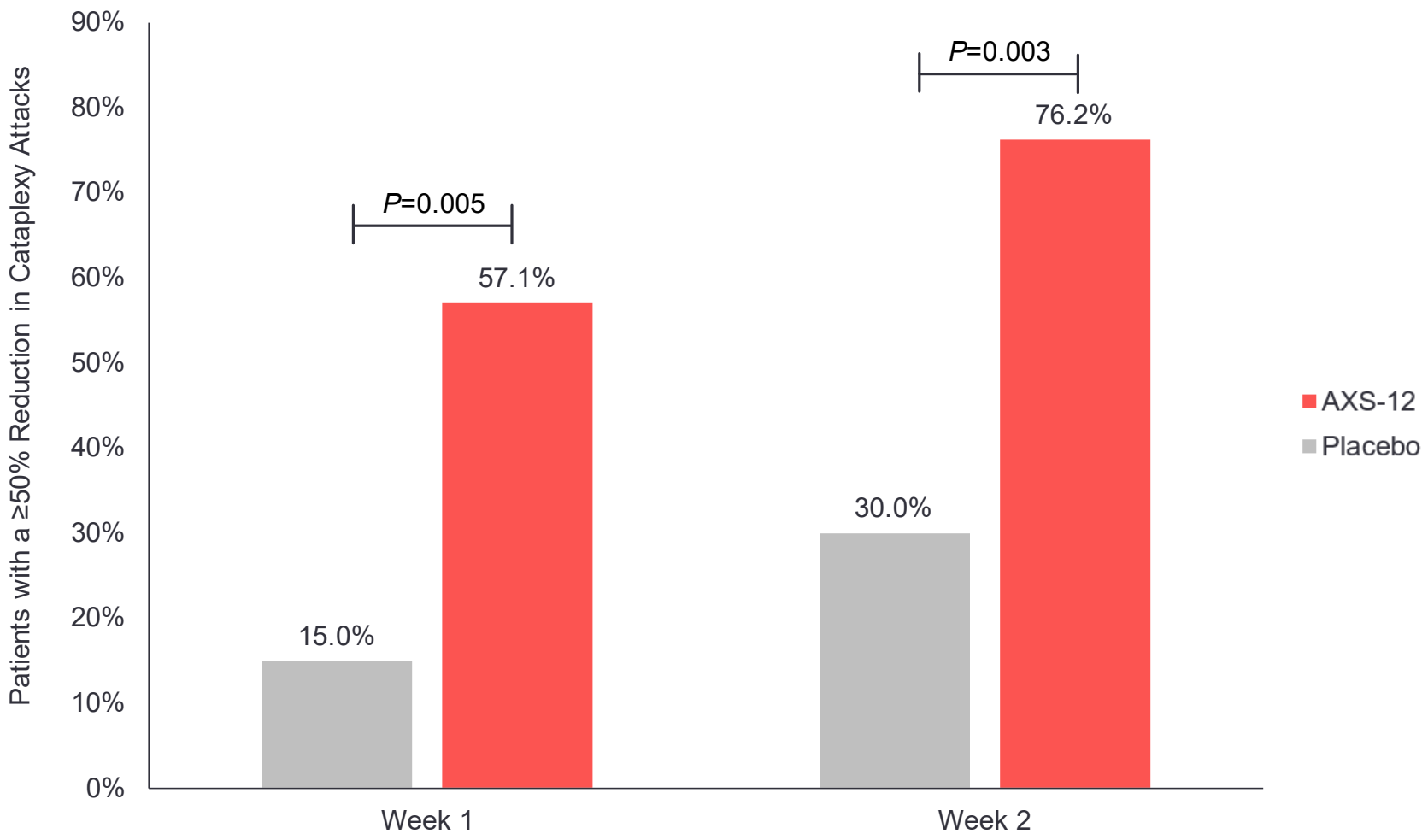
Primary Endpoint: Change in Weekly Cataplexy Attacks



Primary Endpoint	AXS-12	Placebo	P-value
Overall Change in Average Weekly Cataplexy Attacks	-13.0	-0.3	<0.001
Week 2 Change in Average Weekly Cataplexy Attacks	-14.6	-2.6	0.002

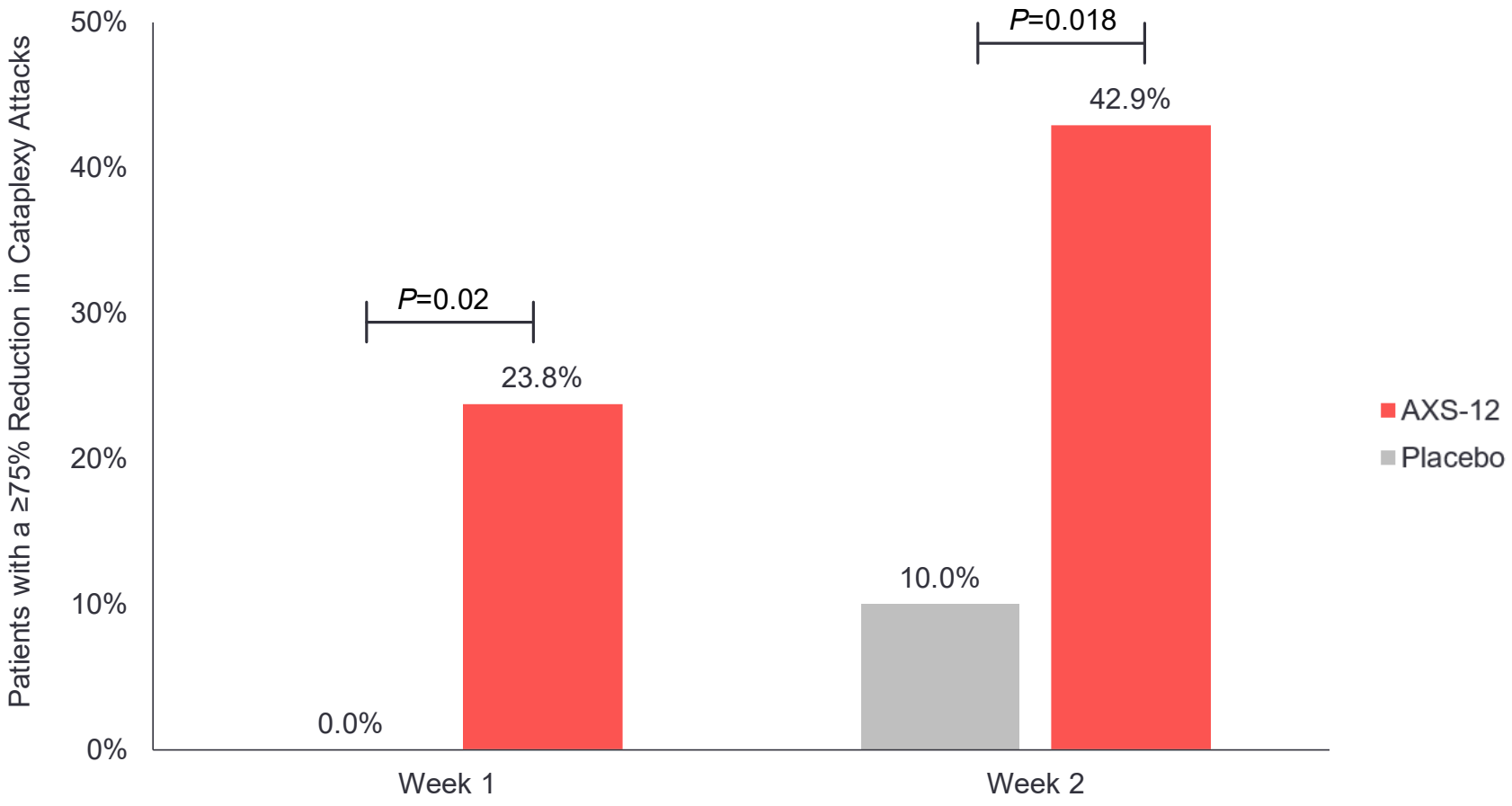
Improved Cataplexy:

Patients with 50% or Greater Reduction in Cataplexy Attacks



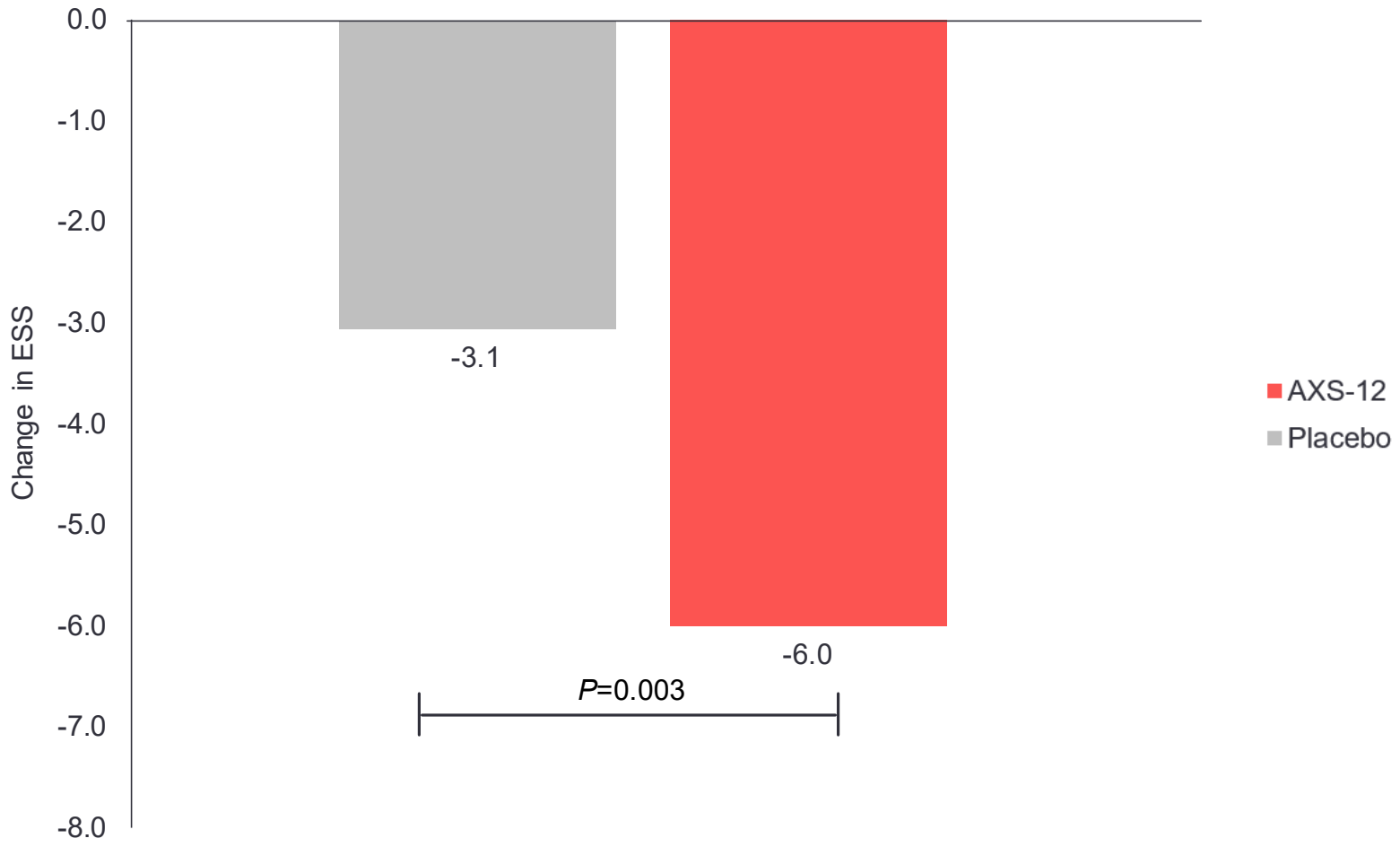
Improved Cataplexy:

Patients with 75% or Greater Reduction in Cataplexy Attacks



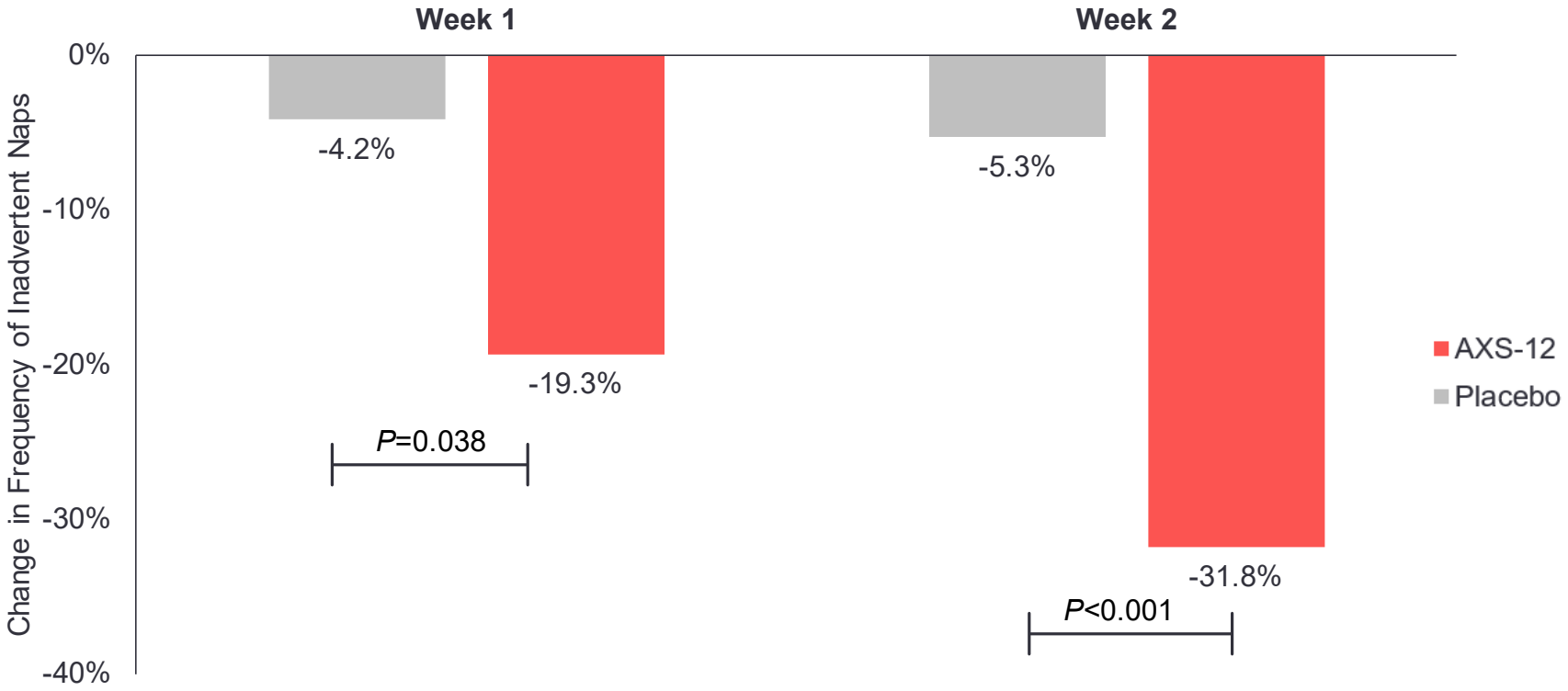
Improved Daytime Sleepiness:

Change in Epworth Sleepiness Scale (ESS) Score



Improved Daytime Sleepiness:

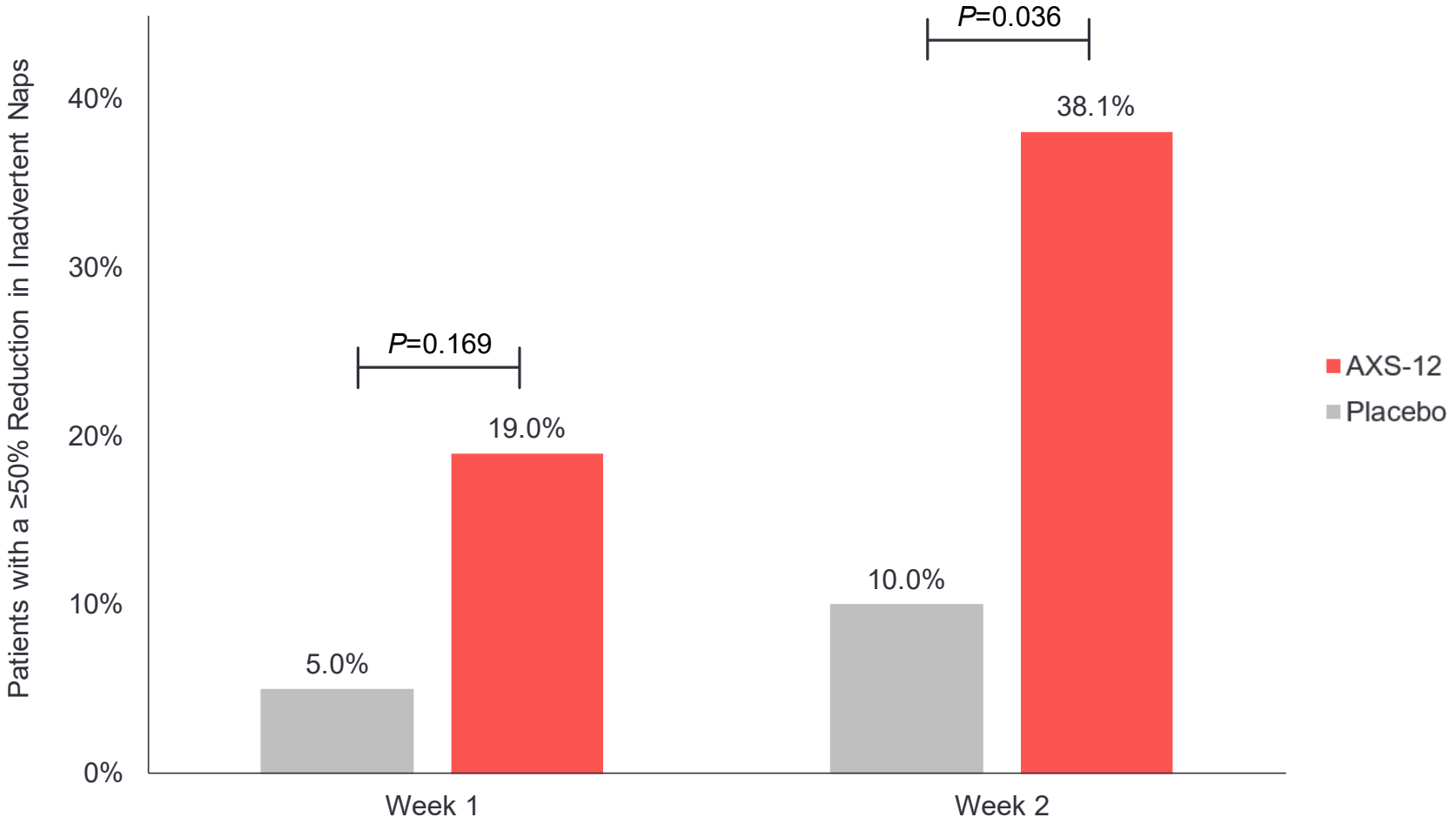
Reduction in the Weekly Frequency of Inadvertent Naps



Change in Weekly Mean Number of Inadvertent Naps	AXS-12	Placebo	P-value
Week 1	-3.57	-0.77	0.038
Week 2	-5.88	-0.98	<0.001

Improved Daytime Sleepiness:

Patients with 50% or Greater Reduction in Inadvertent Naps



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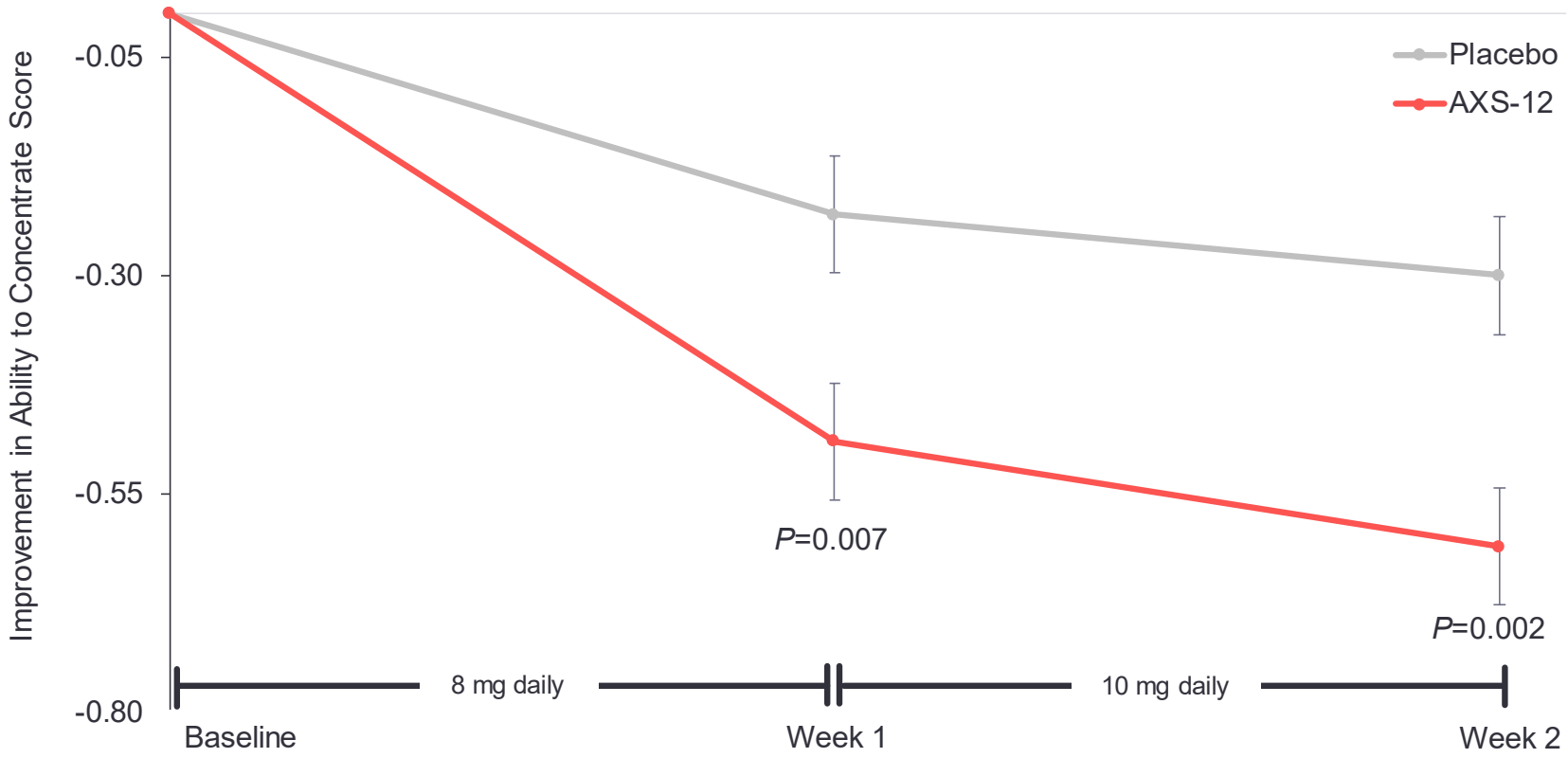
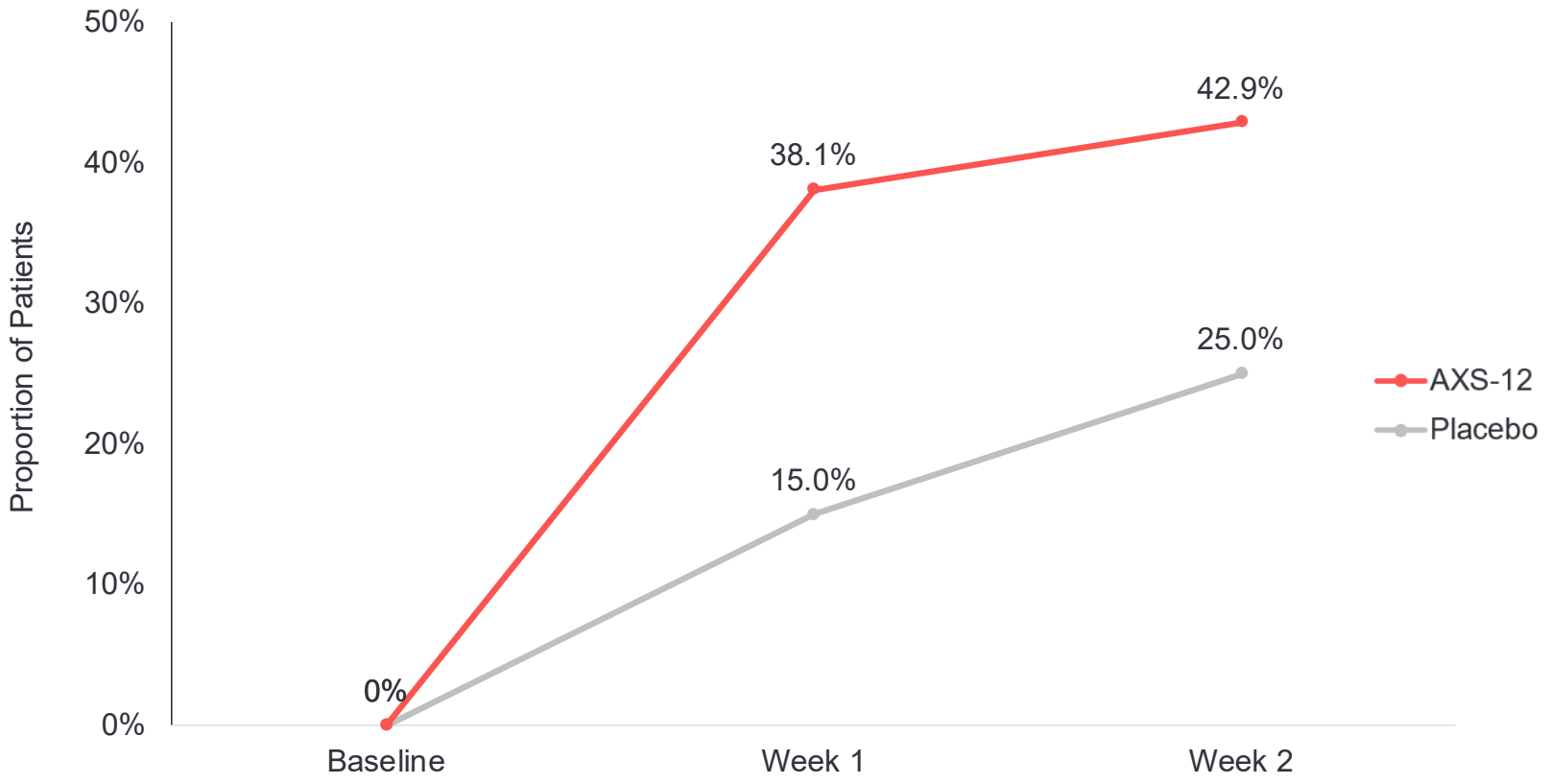
Improved Cognitive Function:
Improvement in Ability to Concentrate Score



- Ability to concentrate was collected daily on a 5-point scale where 1= very good, 2 = good, 3 = average, 4 = poor, 5 = very poor.

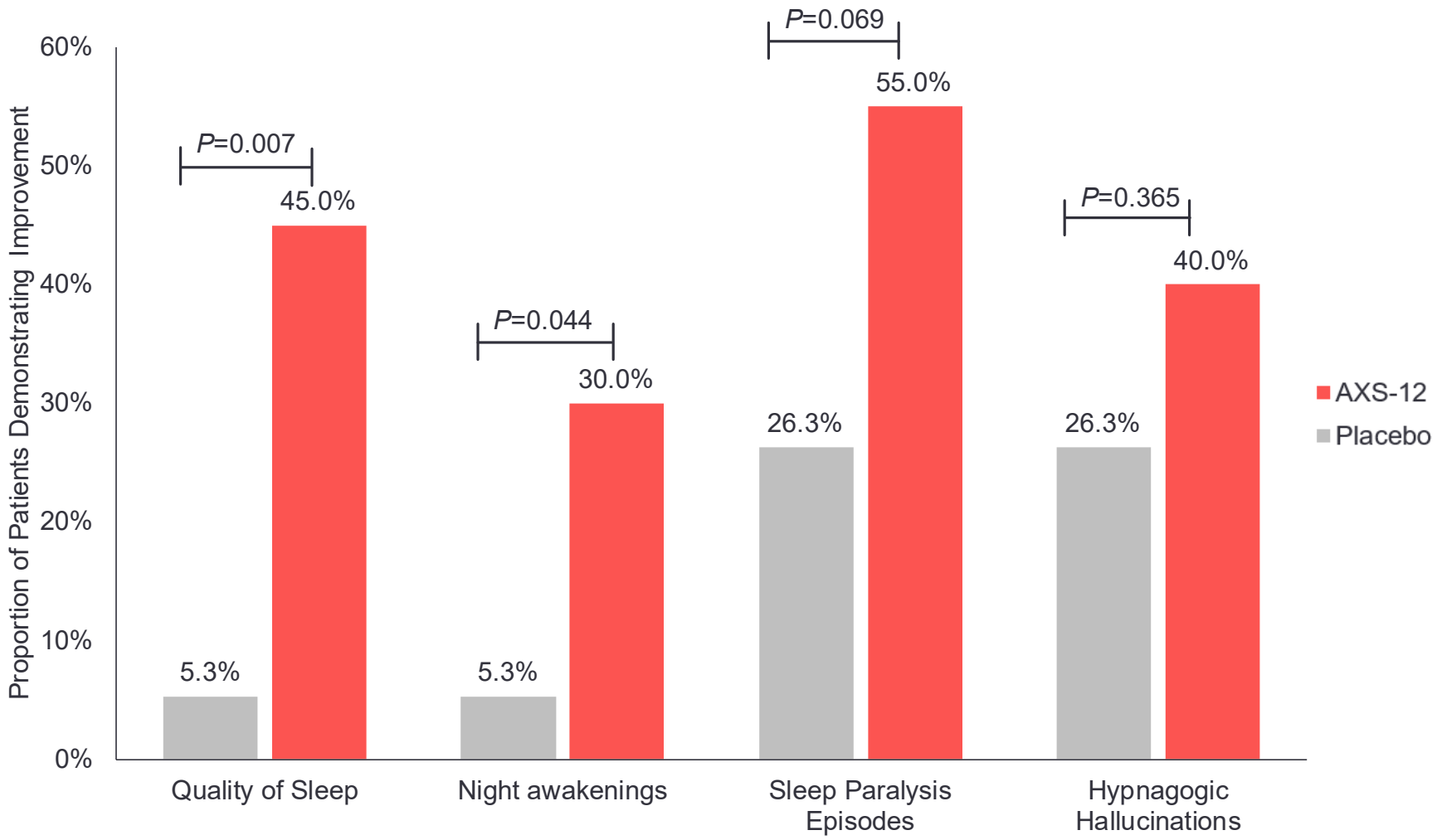
Improved Cognitive Function:

Patients with *Very Good* or *Good* Ability to Concentrate



Improved Sleep Quality:

Sleep Quality & Sleep-Related Symptoms



Safety and Tolerability

- AXS-12 was safe and well tolerated
- No serious adverse events
- No discontinuations due to adverse events
- The overall percentage of patients experiencing adverse events was 42.9% with AXS-12 treatment and 40.0% with placebo
- The most commonly reported adverse events with AXS-12 treatment were anxiety, constipation, and insomnia

CONCERT Trial:
Summary

- AXS-12 met the pre-specified primary endpoint by significantly reducing the frequency of cataplexy attacks compared to placebo
- AXS-12 also demonstrated significant improvements compared to placebo in symptoms of excessive daytime sleepiness
- AXS-12 demonstrated improvements in cognitive function, sleep quality and other sleep-related symptoms
- AXS-12 was safe and well tolerated in this study with no serious adverse events and no discontinuations due to adverse events

Q&A

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Concluding Remarks

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

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Thank you.

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