Frontiers in Brain Health R&D Day

July 21, 2025

Forward Looking Statements & Safe Harbor

Certain matters discussed in this presentation are “forward-looking statements”. The Company may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the commercial success of the Company’s SUNOSI®, AUVELITY®, and SYMBRAVO® products and the success of the Company’s efforts to obtain any additional indication(s) with respect to solriamfetol and/or AXS-05; the Company’s ability to maintain and expand payer coverage; the success, timing and cost of the Company’s ongoing clinical trials and anticipated clinical trials for the Company’s current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including the Company’s ability to fully fund the Company’s disclosed clinical trials, which assumes no material changes to the Company’s currently projected revenues or expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of the Company’s ongoing clinical trials, and/or data readouts, and the number or type of studies or nature of results necessary to support the filing of a new drug application (“NDA”) for any of the Company’s current product candidates; the Company’s ability to fund additional clinical trials to continue the advancement of the Company’s product candidates; the timing of and the Company’s ability to obtain and maintain U.S. Food and Drug Administration (“FDA”) or other regulatory authority approval of, or other action with respect to, the Company’s product candidates, including statements regarding the timing of any NDA submission; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the Company’s ability to successfully resolve any intellectual property litigation, and even if such disputes are settled, whether the applicable federal agencies will approve of such settlements; the successful implementation of the Company’s research and development programs and collaborations; the success of the Company’s license agreements; the acceptance by the market of the Company’s products and product candidates, if approved; the Company’s anticipated capital requirements, including the amount of capital required for the commercialization of SUNOSI, AUVELITY, and SYMBRAVO and for the Company’s commercial launch of its other product candidates, if approved, and the potential impact on the Company’s anticipated cash runway; the Company’s ability to convert sales to recognized revenue and maintain a favorable gross to net sales; unforeseen circumstances or other disruptions to normal business operations arising from or related to domestic political climate, geo-political conflicts or a global pandemic and other factors, including general economic conditions and regulatory developments, not within the Company’s control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstances.

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Jeffrey Cummings, MD, ScD

Joy Chambers-Grundy Professor of Brain Science | Chair of the Chambers-Grundy Center for Transformative Neuroscience | Clinical Professor of Neurology

| *UNLV Department of Brain Health*

Andrew Cutler, MD

Clinical Associate Professor of Psychiatry

| *SUNY Upstate Medical University*

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Professor of Psychiatry & Behavioral Neuroscience | Chief Research Officer and Director of Psychopharmacology Research at the Lindner Center of Hope

| *University of Cincinnati*

Michael Thorpy, MD

Professor of Neurology | Director of the Sleep-Wake Disorders Center at the Montefiore Medical Center

| *Albert Einstein College of Medicine*

Stewart J. Tepper, MD

Vice President at the New England Institute for Neurology | Professor of Neurology

| *Geisel School of Medicine at Dartmouth*

Today's KOL speakers

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11:00 – 11:15 AM	**Welcome and opening remarks**
	Herriot Tabuteau, MD | Founder and Chief Executive Officer | *Axsome* Mark Jacobson, MA | Chief Operating Officer | *Axsome*
11:15 – 12:05 PM	**AXS-05 (dextromethorphan-bupropion)**
11:15 AM	**Alzheimer's disease agitation** Jeffrey Cummings, MD, ScD | Joy Chambers-Grundy Professor of Brain Science; Chair, Chambers-Grundy Center for Transformative Neuroscience; Clinical Professor of Neurology | *UNLV Department of Brain Health*
11:50 AM	**Smoking cessation** Sue Giordano, PhD | Senior Vice President, Medical Affairs | *Axsome*
12:30 – 1:50 PM	**Solriamfetol**
12:30 PM	**Attention deficient hyperactivity disorder** **Major depressive disorder with excessive daytime sleepiness** **Excessive sleepiness in shift work disorder** Andrew Cutler, MD | Clinical Associate Professor of Psychiatry | *SUNY Upstate Medical University*
1:15 PM	**Binge eating disorder** Susan McElroy, MD | Professor of Psychiatry & Behavioral Neuroscience; Chief Research Officer and Director of Psychopharmacology Research, Lindner Center of HOPE | *University of Cincinnati*

Today's agenda

1:50 PM	**Break**
2:00 – 2:25 PM	**AXS-12 in narcolepsy**
	Michael Thorpy, MD | Professor of Neurology; Director, Sleep-Wake Disorders Center, Montefiore Medical Center | *Albert Einstein College of Medicine*
2:25 – 2:50 PM	**AXS-14 in fibromyalgia**
	Andrea Chadwick, MD, MSc, FASA | Kasumi Arakawa Professor of Anesthesiology, Pain, and Perioperative Medicine, Director, Fibromyalgia and Centralized Pain Exploration (FACE) Lab | *University of Kansas Medical Center*
2:50 – 3:15 PM	**SYMBRAVO®**
	Stewart J. Tepper, MD | Vice President | The New England Institute for Neurology and Headache and Professor of Neurology | *Geisel School of Medicine at Dartmouth*
3:15 PM	**Closing remarks**
	Herriot Tabuteau, MD | Founder and Chief Executive Officer | *Axsome*

Today's agenda cont.

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Opening remarks

Herriot Tabuteau, MD

Chief Executive Officer

At Axsome, we are defining the future of clinical practice in brain health

Our mission

is to develop and deliver ***transformative medicines*** for the hundreds of millions of people impacted by central nervous system conditions

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We deliver innovation in conditions with high unmet need, strong value creation potential, and clear strategic fit

Psychiatry

- Depression
- Alzheimer's disease agitation
- Smoking cessation
- ADHD
- Binge eating disorder

Neurology

- Obstructive sleep apnea
- Narcolepsy
- Migraine
- Fibromyalgia
- Shift work disorder

Our strategy positions us to advance the frontiers in brain health and deliver innovation for patients

Deliver **novel mechanisms of action**

Develop **first-in-class or best-in-class** medicines

Apply **precision-based** approaches in **novel, underserved** indications

Enabled by **clinical research and regulatory innovation**

Leverage our **deep expertise** in neuroscience

New frontiers in depression

AUVELITY®

Major depressive disorder

- ***Novel mechanism of action:*** First and only rapid-acting oral NMDA receptor antagonist for the treatment of MDD
- ***FDA breakthrough therapy*** designated
- ***Over 190,000*** new patients reached since launch in October 2022
- ***>$400M*** annual run rate in 3rd full year of launch

$1-$3B peak sales potential

Solriamfetol

MDD with excessive daytime sleepiness

- ***Novel indication*** identified through a precision approach based on clinical presentation and underlying pathophysiology
- ***Initiation*** of Phase 3 trial anticipated in 2025

$1-$1.5B peak sales potential

New frontiers in Alzheimer's disease

AXS-05

Alzheimer's disease agitation

- ***Novel mechanism of action:*** Oral NMDA receptor antagonist for the treatment of Alzheimer's disease agitation
- Potentially ***first-in-class*** medicine
- ***Novel*** indication
- ***FDA breakthrough therapy*** designated
- ***Three*** completed positive registrational trials
- ***sNDA submission*** on track for 3Q 2025

$1.5-$3B peak sales potential

New frontiers in sleep and cognition

AXS-12

Narcolepsy

- ***Novel mechanism of action:*** Highly selective NRI and dopamine modulator
- ***First-in-class*** precision-based mechanism targeting underlying neurotransmitter deficit
- Significant ***improvements*** in cognitive function in three completed, positive registrational trials
- ***NDA submission*** anticipated in 2H 2025

$0.5-$1B peak sales potential

Solriamfetol

Excessive sleepiness in shift work disorder

- ***Novel mechanism of action:*** DNRI and TAAR1 agonist
- Significant ***improvements*** in cognitive function in SHARP study in cognitively impaired patients with EDS
- ***Topline results*** of Phase 3 trial anticipated in 2026

$0.3-$0.5B peak sales potential

New frontiers in brain health

		Indication	Innovation	Development stage	Peak sales
Psychiatry	Auvelity® (dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg	**Major depressive disorder**	First-in-class MOA, FDA Breakthrough therapy	In-market	**$1-$3B**
	AXS-05 *(dextromethorphan-bupropion)* NMDA antagonist, sigma-1 agonist, and aminoketone CYP2D6 inhibitor	**Alzheimer's disease agitation**	First-in-class MOA, FDA Breakthrough therapy	NDA-stage	**$1.5-$3B**
		Smoking cessation	First-in-class MOA	Phase 3	**$0.5-$1B**
	Solriamfetol DNRI , TAAR1 agonist, 5-HT_{1A} agonist	**ADHD**	Novel MOA	Phase 3	**$1-$3B**
		MDD with EDS	Novel MOA, precision-driven targeting	Phase 3	**$1-$1.5B**
		Binge eating disorder	Novel indication	Phase 3	**$0.5-$1B**
Neurology	SUNOSI (solriamfetol) (V)	**EDS in narcolepsy or OSA**	First-in-class, best-in-class MOA	In-market	**$0.3-$0.5B**
	SYMBRAVO® (meloxicam and rizatriptan) 20 mg/10 mg tablets	**Migraine**	MoSEIC™ technology-enabled NCE	In-market	**$0.5-$1B**
	AXS-12 *(reboxetine)* Highly selective NRI, dopamine mod.	**Narcolepsy**	Novel MOA, pro-cognitive	NDA-stage	**$0.5-$1B**
	AXS-14 *(esreboxetine)* [S,S]-enantiomer of AXS-12	**Fibromyalgia**	Best-in-class MOA, addresses fatigue	Phase 3	**$0.5-$1B**
	Solriamfetol DNRI , TAAR1 agonist, 5-HT_{1A} agonist	**Shift work disorder**	Best-in-class MOA	Phase 3	**$0.3-$0.5B**

Advancing novel medicines with the potential to deliver significant long-term value to patients and shareholders

>$16B peak sales potential

>150M patients

Issued patents extending out to early **2040s**

We are defining the future of clinical practice in brain health

axsome

AXS-05

Jeffrey Cummings, MD, ScD

Joy Chambers-Grundy Professor of Brain Science | Chair of Chambers-Grundy Center for Transformative Neuroscience | Clinical Professor of Neurology

| *UNLV Department of Brain Health*

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ADVANCING FRONTIERS IN ALZHEIMERS AGITATION: First-in-class MOA, novel indication

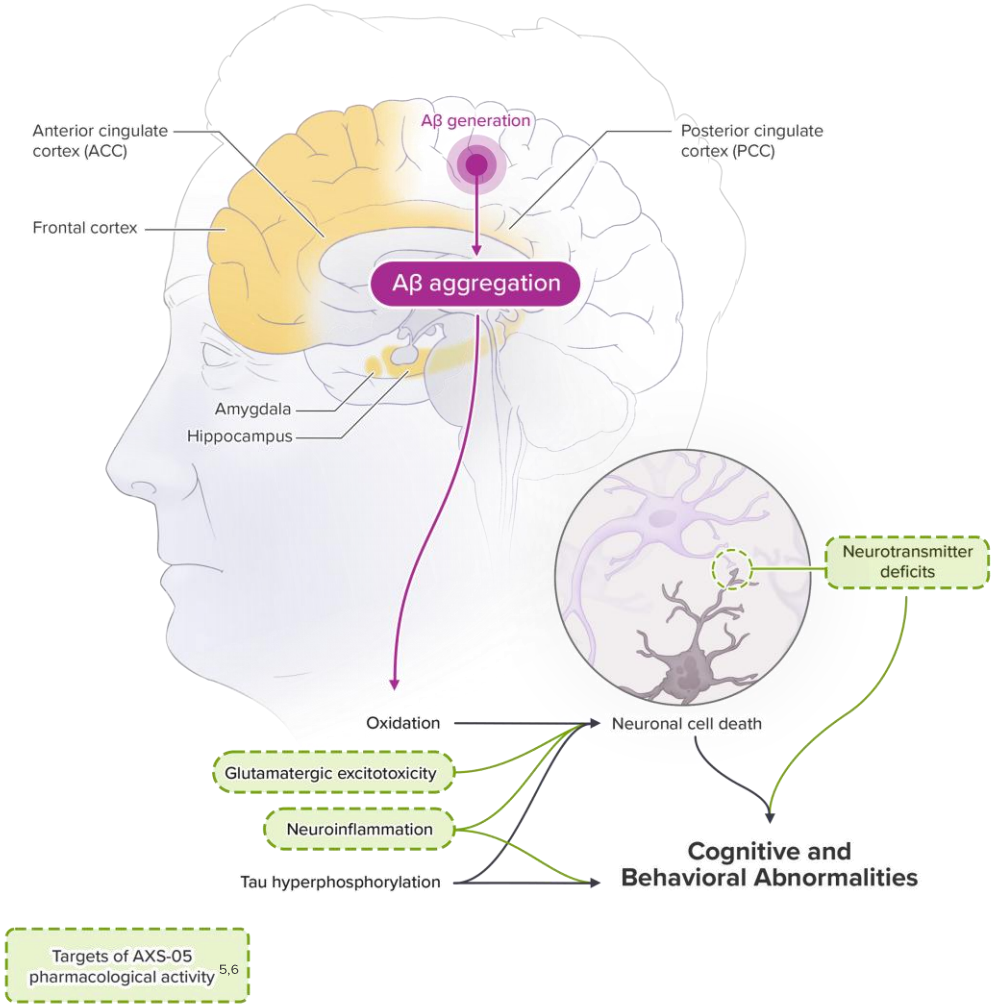
AXS-05 (dextromethorphan-bupropion)

Potentially first-in-class, best-in-class treatment for Alzheimer's disease agitation

In Alzheimer's disease, insoluble Aβ production and accumulation *triggers secondary steps* leading to synaptic loss and neuronal cell death[1,2]

Reductions in certain *neurotransmitters* are thought to contribute to cognitive and behavioral symptoms including agitation and aggression[1-4]

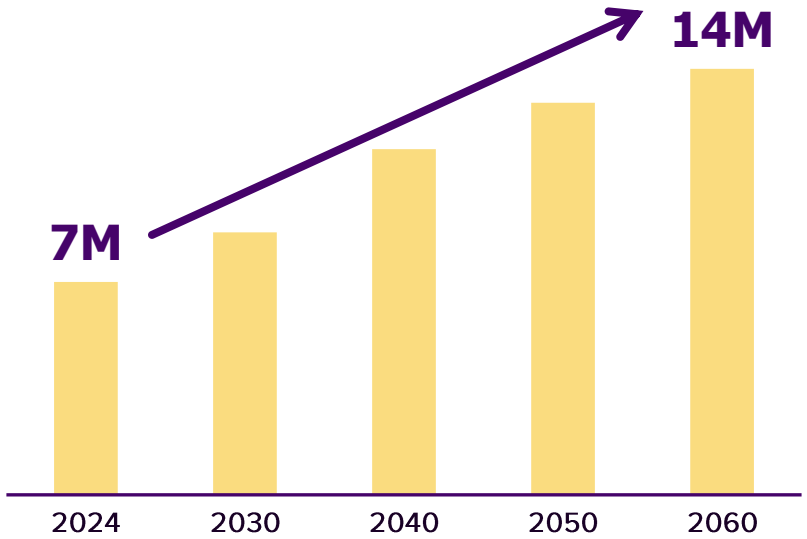
AXS-05 *modulates the function* of neurotransmitters and receptors implicated in Alzheimer's disease (glutamate, sigma-1, norepinephrine, and dopamine)[1-4]



1. Cummings JL, *N Engl J Med.* 2004; 2. Querfurth HW & LaFerla FM, *N Engl J Med.* 2010; 3. Porsteinsson AP & Antonsdottir IM, *Expert Opin Pharmacother.* 2017; 4. Rosenberg PB, Nowrangi MA, & Lyketsos CG, *Mol Aspects Med.* 2015; 5. Stahl SM, *CNS Spectr.* 2019; 6. Cheng W, et al. *Mol Med Rep.* 2015

Alzheimer's disease (AD) agitation

Number of U.S. adults aged 65+ with Alzheimer's dementia expected to double by 2060[1]



Alzheimer's disease (AD) is the most common form of dementia, affecting over ***7M*** people in the U.S.[1]

Agitation is one of the most common and debilitating neuropsychiatric symptoms affecting up to ***76%*** of people[1,2]

AD agitation is characterized by emotional distress, verbal and physical aggressiveness, disruptive irritability, and disinhibition[1,2]

1. 2025 Alzheimer's Disease Facts and Figures; 2. Trachtenberg et al. *J Neuropsychiatry Clin Neurosci.* 2002

Agitation is a common behavioral symptom and may present across stages of Alzheimer's disease[1,2]

Agitation encompasses three broadly defined symptom domains including both non-aggressive and aggressive behaviors[3,4]

Excessive motor activity behaviors

- Pacing
- Rocking
- Gesturing
- Pointing fingers
- Restlessness
- Performing repetitious mannerisms

Verbal aggression behaviors

- Yelling
- Speaking in an excessively loud voice
- Using profanity
- Screaming
- Shouting

Physical aggression behaviors

- Grabbing
- Shoving
- Pushing
- Resisting
- Hitting others
- Kicking objects or people
- Scratching
- Biting
- Throwing objects
- Hitting self
- Slamming doors
- Tearing things
- Destroying property
- Grabbing

Prevalence of agitation across AD severity[5]: **56%** **Mild** **75%** **Moderate-to-severe** **68%** **Severe**

AD = Alzheimer's disease

1. 2025 Alzheimer's Disease Facts and Figures; 2. Tractenberg RE, et al. *J Neuropsychiatry Clin Neurosci.* 2002; 3. Cummings J, et al. *Int Psychogeriatr.* 2015; 4. Sano M, et al. *Int Psychogeriatr.* 2023; 5. Halpern R, et al. *Int J Geriatr Psychiatry* 2018

The CMAI questionnaire assesses a broad range of agitated behaviors consistent with the four IPA criteria[1]

Cohen-Mansfield Agitation Inventory (CMAI)

29 agitated behaviors organized into four subscales

Physically aggressive

- Hitting
- Kicking
- Grabbing
- Pushing
- Scratching
- Biting
- Hurting oneself or others
- Spitting
- Tearing things
- Throwing things
- Falling intentionally
- Physical sexual advances

Physically non-aggressive

- Pacing
- Inappropriate dressing and/or disrobing
- Inappropriate eating or drinking
- Exit-seeking behaviors
- Hiding things
- Handling things inappropriately
- Hoarding
- Repetitious mannerisms
- Restlessness

Verbally aggressive

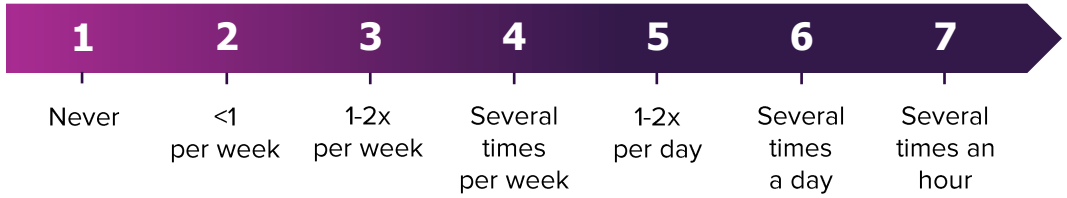
- Cursing
- Making strange noises
- Screaming
- Making verbal sexual advances

Verbally non-aggressive

- Attention-seeking behaviors
- Complaining
- Negativism
- Repetitive sentences or questions

Individual agitated behavior scores

Frequency of each behavior is rated on a 7-point scale



CMAI total score

Sum of individual behavior scores for all items in the CMAI

1. Cohen-Mansfield J. *J Psychiatr Res.* 2008

Agitation worsens impact of Alzheimer's disease and adds significant burden on patient and caregiver

Agitation in patients with Alzheimer's disease is associated with[1-3]:

Accelerated disease progression and cognitive decline

Earlier institutionalization and *higher risk* of LTC placement

Increased fall and mortality risk

Greater health care utilization

Increased caregiver burden

Greater concomitant medication use, including antipsychotics

Poor quality of life for patients and caregivers

LTC = long-term care

1. Porsteinsson AP & Antonsdottir IM. *Expert Opin Pharmacother.* 2017; 2. Fillit H, et al. *Int J Geriatr Psychiatry* 2021; 3. Jones E, et al. *J Alzheimers Dis.* 2021

Unmet need in the treatment of agitation associated with Alzheimer's disease

Agitation affects the majority of patients with Alzheimer's disease and is one of the most troubling and consequential aspects of Alzheimer's disease for patients and caregivers[1,2]

Current pharmacologic treatments are primarily off-label medications:

- Typical and atypical antipsychotics, benzodiazepines, antiepileptics, antidepressants
- About ½ of treated patients are on more than one class of medication[3]

Limitations of off-label medications:

- Sedation, extrapyramidal side effects, falls, worsening of cognition, cardiovascular and cerebrovascular events
- Black box warning for increased mortality risk in elderly patients with dementia
- Modest efficacy

Only 1 FDA-approved agent, an atypical antipsychotic

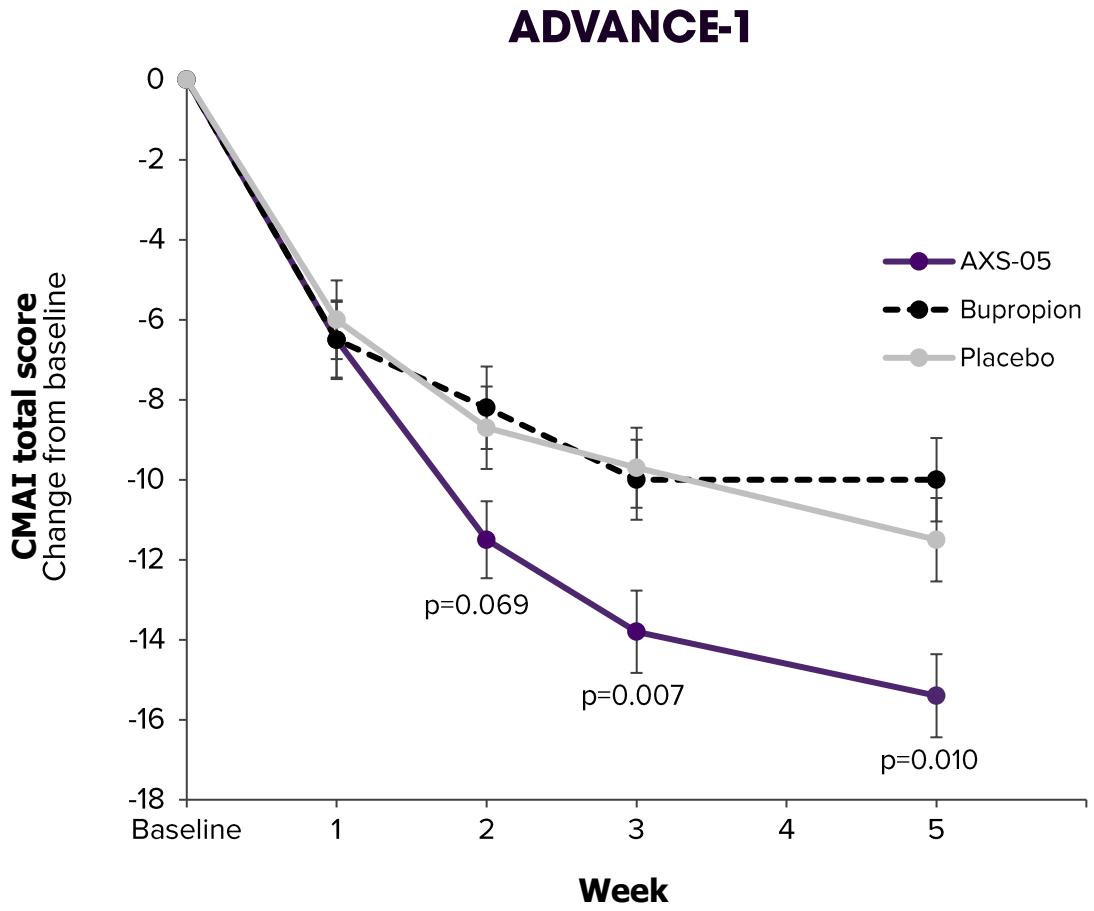
There is an urgent unmet need for new effective pharmacological treatments with favorable safety and tolerability

1. 2025 Alzheimer's Disease Facts and Figures; 2. Trachtenberg et al. *J Neuropsychiatry Clin Neurosci.* 2002; 3. Veeva Compass Claims Data.

Comprehensive Phase 3 clinical program of AXS-05 in Alzheimer's disease agitation

ADVANCE-1	ADVANCE-2	ACCORD-1	ACCORD-2
Phase 2/3 (N=366)	*Phase 3 (N=408)*	*Phase 3 (N=108)*	*Phase 3 (N=167)*
Randomized, double-blind, active & placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized withdrawal, double-blind, placebo-controlled	Randomized withdrawal, double-blind, placebo-controlled
45 mg/105 mg twice daily	45 mg/105 mg twice daily	45 mg/105 mg twice daily	45 mg/105 mg twice daily
5 weeks	5 weeks	Up to 26 weeks	Up to 24 weeks
Primary endpoint: Change from baseline in the CMAI total score at Week 5	**Primary endpoint:** Change from baseline in the CMAI total score at Week 5	**Primary endpoint:** Time from randomization to relapse of agitation **Relapse criteria:** ≥10 point increase (worsening) in the CMAI for 2 consecutive weeks or a CMAI total score ≥ baseline CMAI for 2 consecutive weeks	**Primary endpoint:** Time from randomization to relapse of agitation **Relapse criteria:** ≥10 point increase (worsening) in the CMAI for 2 consecutive weeks or a CMAI total score ≥ baseline CMAI for 2 consecutive weeks

Rapid and statistically significant improvements in Alzheimer's disease agitation



Rapid and substantial reduction in agitation with separation as early as Week 2 and statistically significant improvement at Week 3

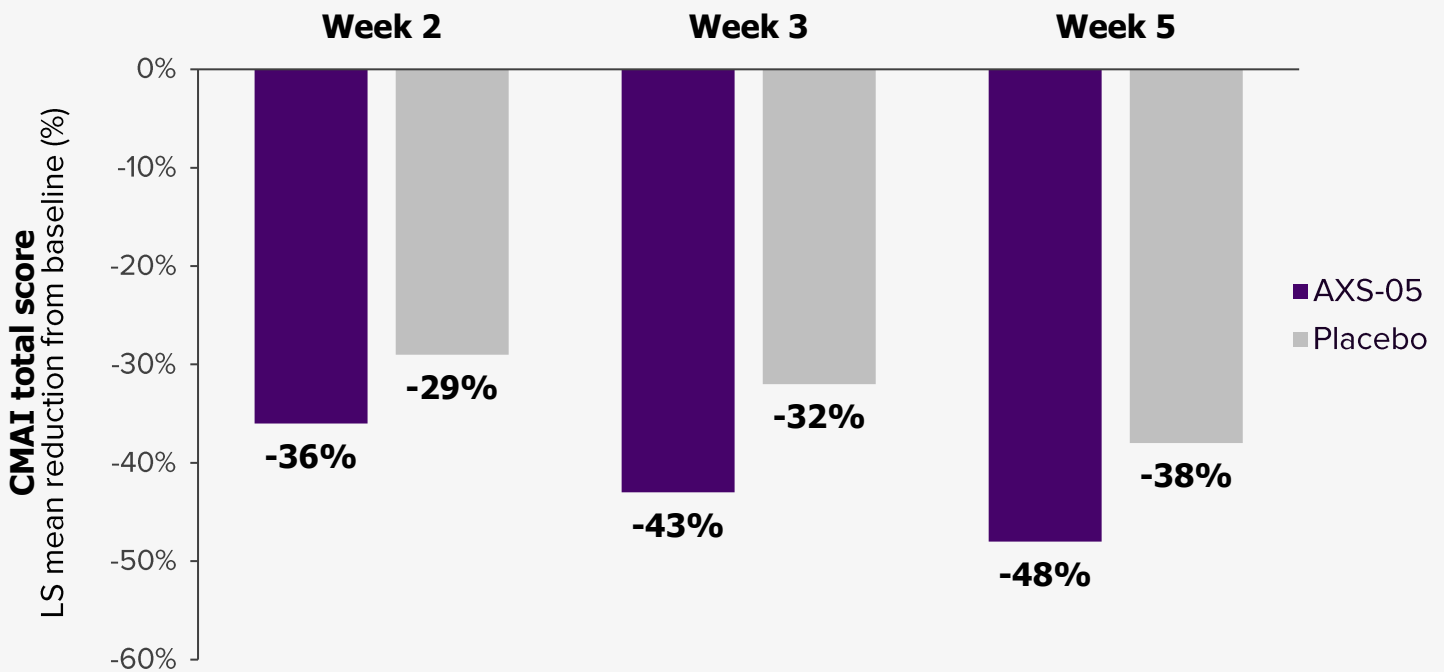
Significantly greater percentage of patients on AXS-05 achieved a clinical response (≥30% reduction in CMAI) vs. placebo (p=0.005)

Well tolerated with **low and similar** TEAE-related discontinuation rates between AXS-05 and placebo groups

Axsome Therapeutics, Inc. Data on file.

Improvements in Alzheimer's disease agitation represent substantial reductions from baseline

ADVANCE-1



Substantial improvements in agitation as measured by the CMAI total score represent a 48% reduction from baseline with AXS-05 treatment

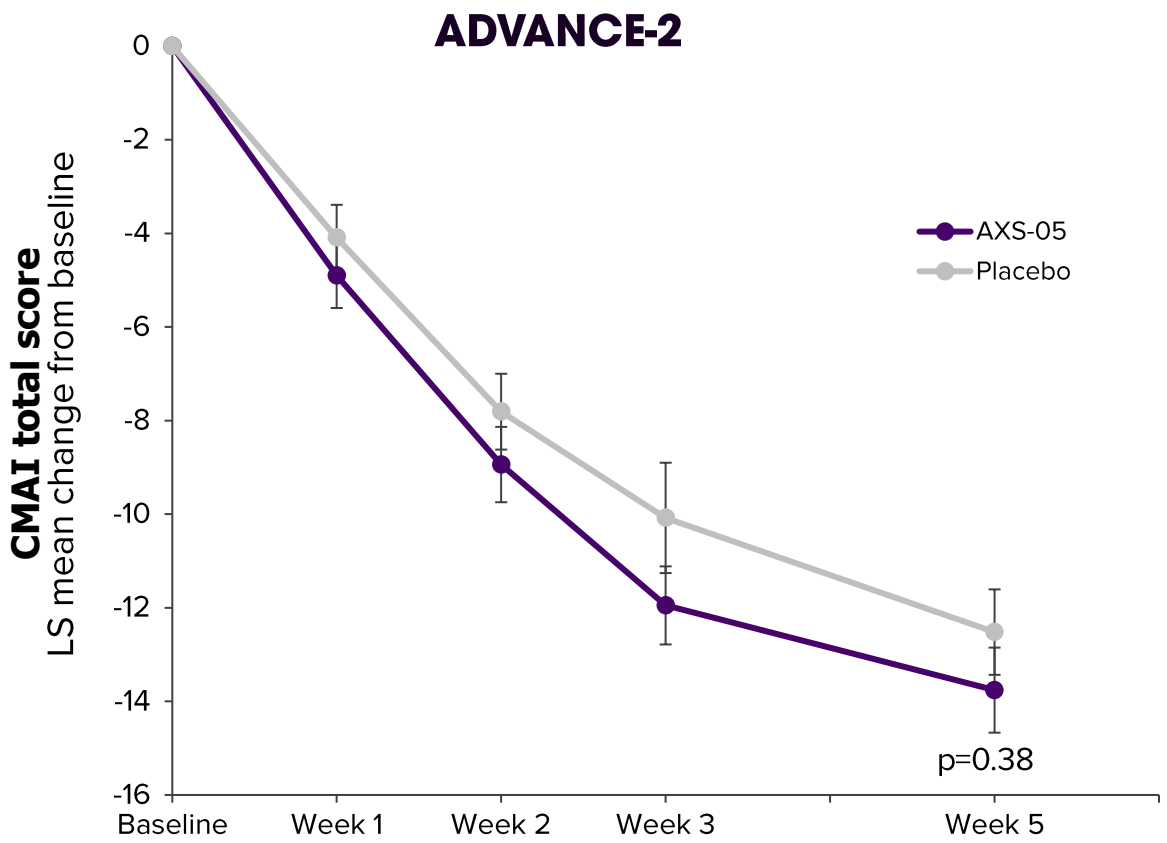
Axsome Therapeutics, Inc. Data on file.

ADVANCE-1 safety summary

Number of patients (%)	AXS-05 (n=159)	Placebo (n=158)
Incidence of TEAEs	70 (44.0)	52 (32.9)
Incidence of serious TEAEs	5 (3.1)	9 (5.7)
Discontinuation due to TEAEs	0 (0.0)	1 (0.6)
Deaths	0 (0.0)	1 (0.6)
Most common TEAEs (≥3% in AXS-05 group)		
Somnolence	13 (8.2)	5 (3.2)
Dizziness	10 (6.3)	5 (3.2)
Diarrhea	7 (4.4)	7 (4.4)
Headache	6 (3.8)	4 (2.5)

Axsome Therapeutics, Inc. Data on file.

Consistent efficacy trend observed in ADVANCE-2 Phase 3 trial



Numerically greater improvement in the CMAI total score vs. placebo demonstrated at all timepoints throughout the trial

Secondary endpoints numerically favored AXS-05 over placebo, consistent with the primary endpoint

Axsome Therapeutics, Inc. Data on file.

ADVANCE-2 safety summary

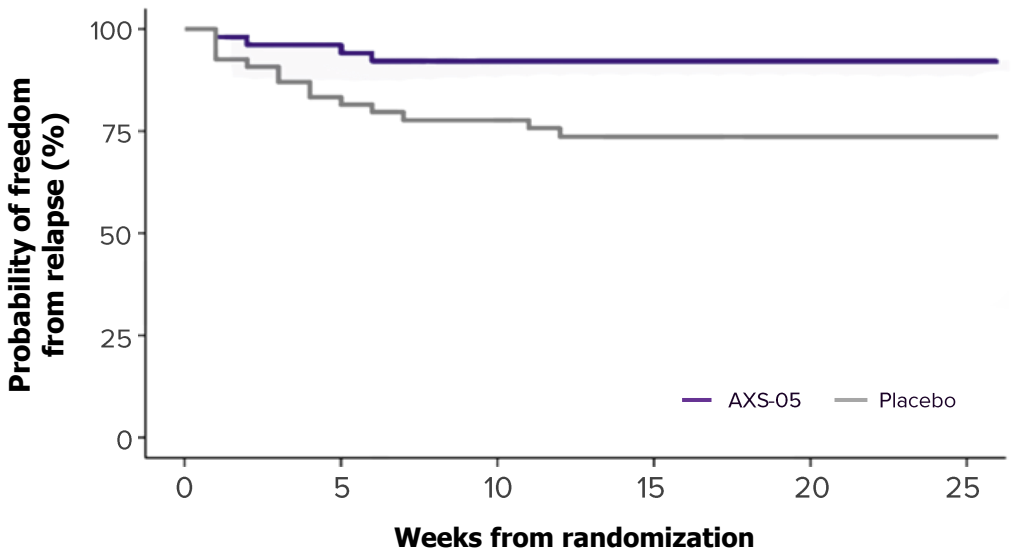
Number of patients (%)	AXS-05 (n=204)	Placebo (n=204)
Incidence of TEAEs	53 (26.0)	44 (21.6)
Incidence of serious TEAEs	2 (1.0)	0 (0.0)
Discontinuation due to TEAEs	3 (1.5)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)
Most common TEAEs (≥3% in AXS-05 group)		
Dizziness	12 (5.9)	3 (1.5)
Headache	9 (4.4)	7 (3.4)

Axsome Therapeutics, Inc. Data on file.

AXS-05 treatment significantly delayed time to relapse of Alzheimer's disease agitation

ACCORD-1

Randomized withdrawal design



Hazard ratio for time to relapse	
Hazard ratio (95% CI)	**0.275** (0.091-0.836)
p-value	0.014

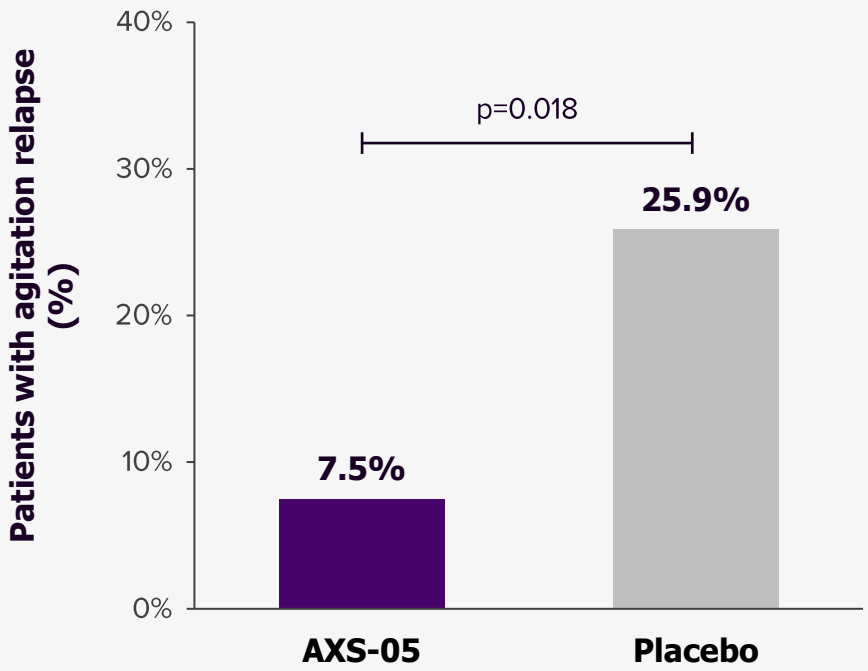
AXS-05 *significantly delayed* time to relapse vs. placebo (p=0.014)

Patients on AXS-05 were *3.6x less likely* to relapse compared to placebo

Axsome Therapeutics, Inc. Data on file.

Prevention of Alzheimer's disease agitation relapse in patients treated with AXS-05

ACCORD-1

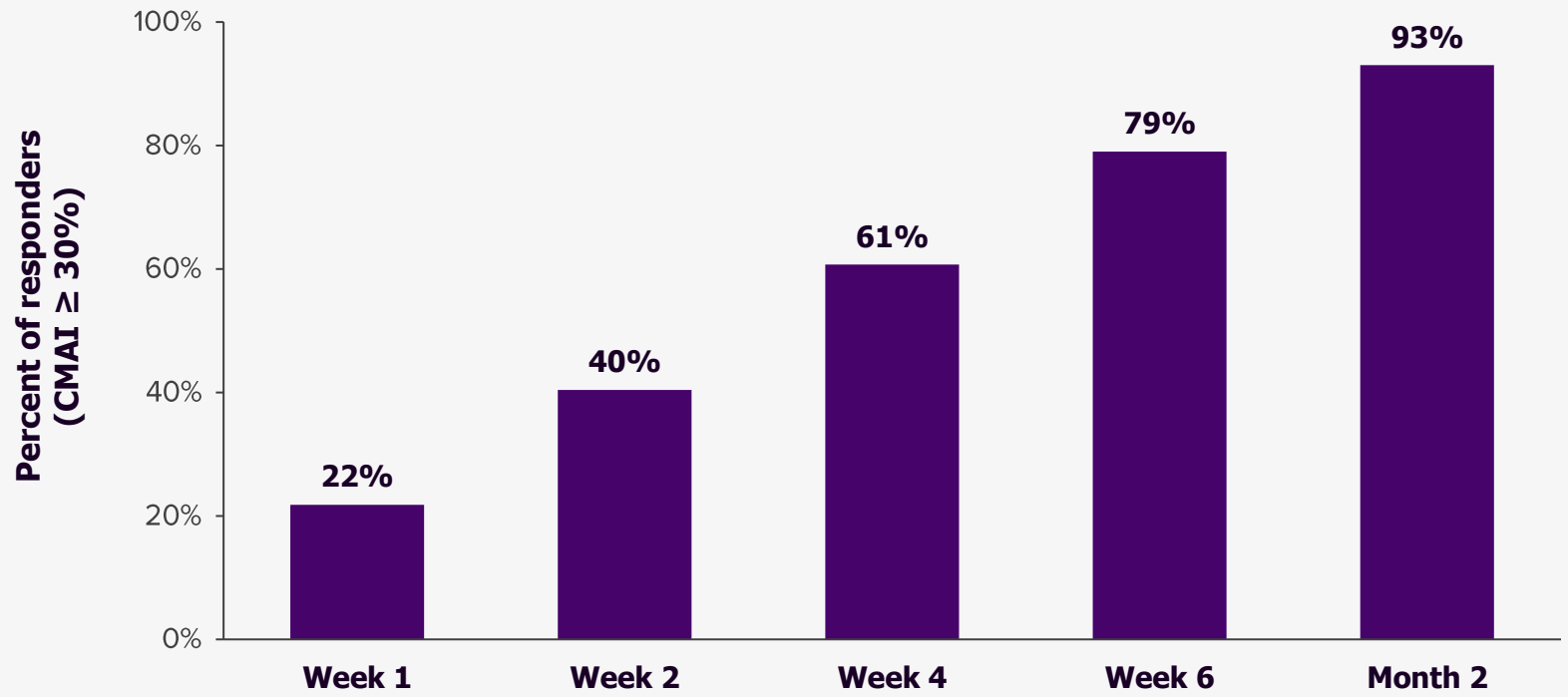


AXS-05 statistically significantly prevented relapse of agitation compared to placebo (p=0.018)

Axsome Therapeutics, Inc. Data on file.

Rapid and durable improvements in Alzheimer's disease agitation with AXS-05 open-label treatment

ACCORD-1



A majority of patients achieved a clinical response (≥30% reduction in CMAI) by week 3 and over 90% by week 7 in the open-label period

Axsome Therapeutics, Inc. Data on file.

ACCORD-1 safety summary

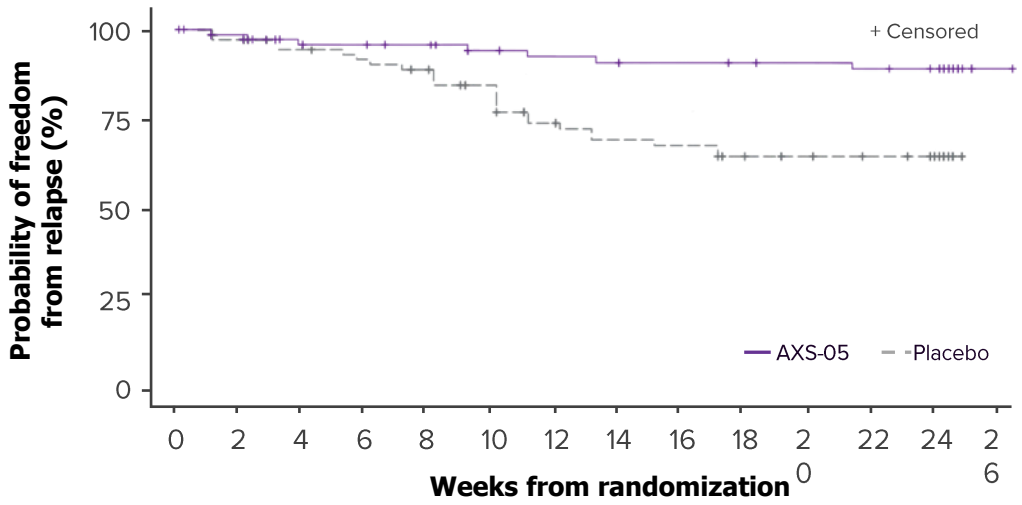
	Double-blind period	
Number of patients (%)	**AXS-05 (n=53)**	**Placebo (n=54)**
Incidence of TEAEs	15 (28.3)	12 (22.2)
Incidence of serious TEAEs	1 (1.9)	2 (3.7)
Discontinuation due to TEAEs	0 (0.0)	1 (1.9)
Most common TEAEs (≥5% in AXS-05 group)		
Diarrhea	4 (7.5)	2 (3.7)
Fall	4 (7.5)	2 (3.7)
Back pain	3 (5.7)	2 (3.7)

Axsome Therapeutics, Inc. Data on file.

Substantially consistent efficacy results demonstrating significant delay in relapse of Alzheimer's disease agitation

ACCORD-2

Randomized withdrawal design



Hazard ratio for time to relapse	
Hazard ratio (95% CI)	**0.276** (0.119-0.641)
p-value	0.001

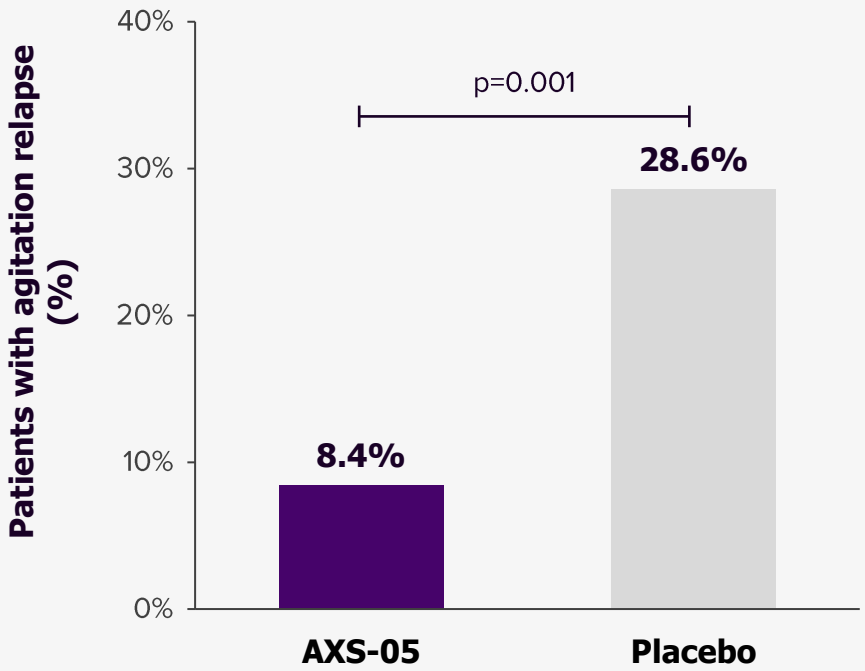
AXS-05 *significantly delayed* time to relapse compared to placebo (p=0.001)

Patients on AXS-05 were *3.6x less likely* to relapse compared to placebo

Axsome Therapeutics, Inc. Data on file.

Relapse prevention of Alzheimer's disease agitation in patients treated with AXS-05

ACCORD-2

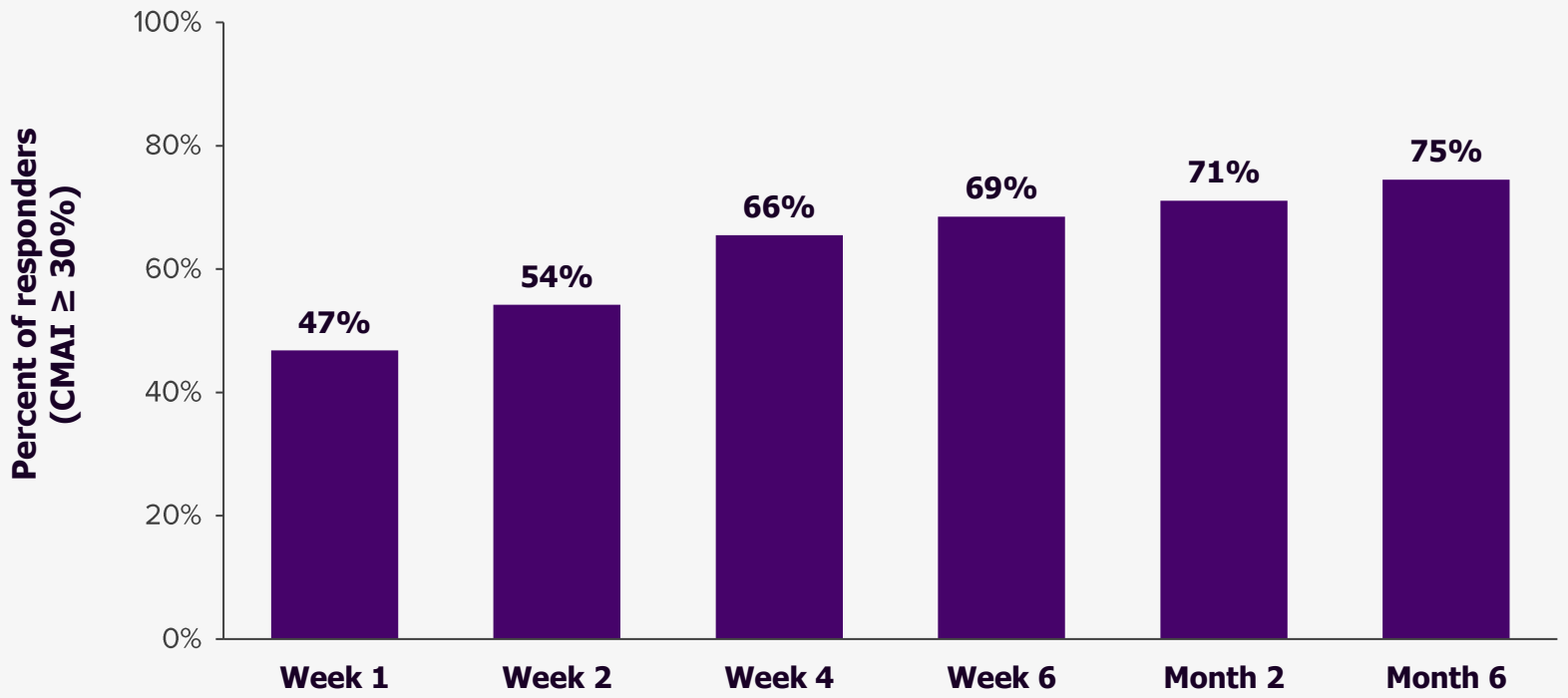


AXS-05 statistically significantly prevented relapse of agitation compared to placebo (p=0.001)

Axsome Therapeutics, Inc. Data on file.

Sustained improvements in Alzheimer's disease agitation symptoms over long-term treatment

ACCORD-2

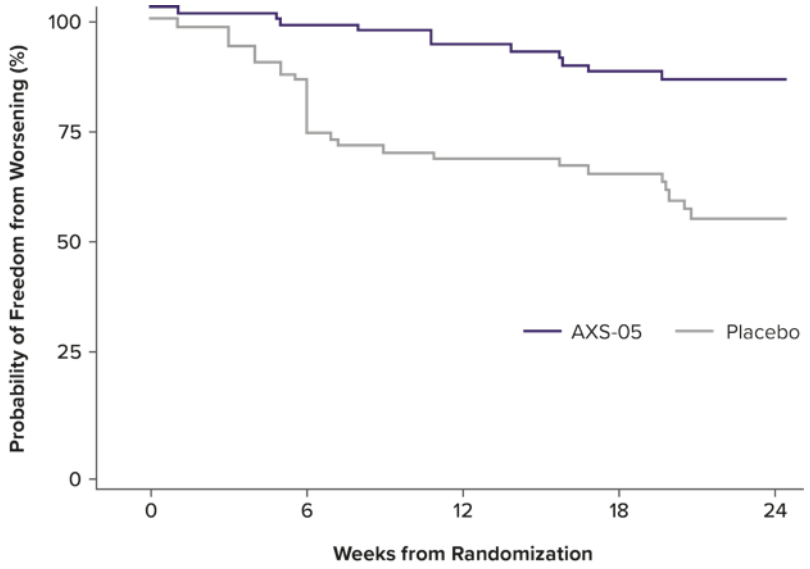


A majority of patients achieved a clinical response (≥30% reduction in CMAI) by week 2, with 75% of patients achieving a clinical response after 6 months of AXS-05 treatment

Axsome Therapeutics, Inc. Data on file.

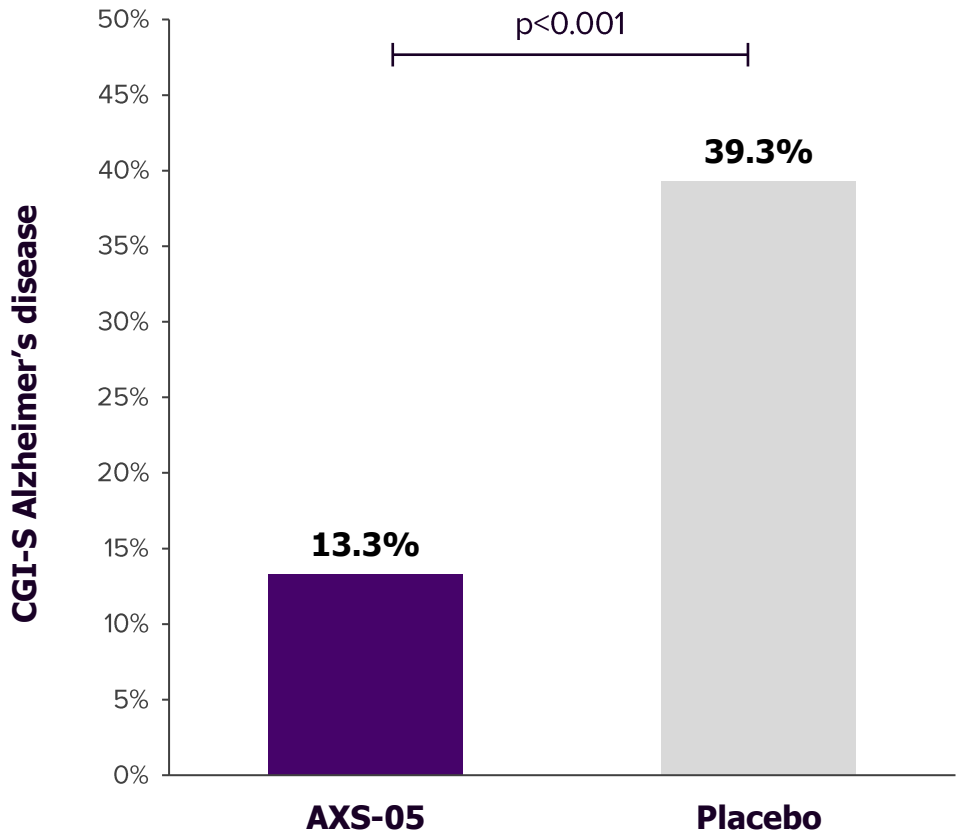
Significant reduction in worsening of Alzheimer's disease severity[1]

Time from randomization to worsening in CGI-S Alzheimer's disease overall clinical status



Hazard ratio for time to relapse	
Hazard ratio (95% CI)	0.272 (0.137-0.540)
p-value	<0.001

Percent of patients with worsening Alzheimer's disease severity



1. ACCORD-2 secondary efficacy analysis. Axsome Therapeutics, Inc. Data on file.

ACCORD-2 safety summary

	Double-blind period	
Number of patients (%)	**AXS-05 (n=82)**	**Placebo (n=84)**
Incidence of TEAEs	24 (29.3)	27 (32.1)
Incidence of serious TEAEs	0 (0.0)	2 (2.4)
Discontinuation due to TEAEs	0 (0.0)	1 (1.2)
Most common TEAEs (≥3% in AXS-05 group)		
Anemia	3 (3.7)	1 (1.2)
Headache	3 (3.7)	2 (2.4)
Hyperkalemia	3 (3.7)	1 (1.2)
Somnolence	3 (3.7)	0 (0.0)

Axsome Therapeutics, Inc. Data on file.

Consistent safety profile observed over long-term treatment

Number of patients (%)	AXS-05 (n=456)
Incidence of TEAEs	182 (39.9)
Incidence of serious TEAEs	12 (2.6)
Discontinuation due to TEAEs	2 (0.4)
Most common TEAEs (≥3%)	
Headache	25 (5.5)
Diarrhea	15 (3.3)
Dizziness postural	14 (3.1)
Fall	14 (3.1)
Hyperkalemia	14 (3.1)
Somnolence	14 (3.1)
Urinary tract infection	14 (3.1)

Axsome Therapeutics, Inc. Data on file.

Four Phase 3 clinical trials support the efficacy of AXS-05 in Alzheimer's disease agitation

ADVANCE-1	ADVANCE-2	ACCORD-1	ACCORD-2
Phase 2/3 (N=366)	*Phase 3 (N=408)*	*Phase 3 (N=108)*	*Phase 3 (N=167)*
Randomized, double-blind, active & placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized withdrawal, double-blind, placebo-controlled	Randomized withdrawal, double-blind, placebo-controlled
Achieved primary endpoint: Statistically significant mean reduction in CMAI total score at Week 5 of 15.4 points for AXS-05 vs. 11.5 points for placebo (p=0.010)	**Primary endpoint:** Mean reduction in CMAI total score at Week 5 of 13.8 points for AXS-05 vs. 12.6 points for placebo	**Achieved primary endpoint:** Statistically significant delay in the time to relapse of agitation; hazard ratio of 0.275 (p=0.014)	**Achieved primary endpoint:** Statistically significant delay in the time to relapse of agitation; hazard ratio of 0.276 (p=0.001)

Axsome Therapeutics, Inc. Data on file.

AXS-05 demonstrated a favorable and differentiated safety profile across four controlled and long-term trials

Low discontinuation rate

<2% of participants receiving AXS-05 discontinued due to adverse events

No deaths reported

No deaths occurred in patients receiving AXS-05 across clinical development program

Not associated with common AEs

AXS-05 was *not associated* with sedation, falls, or cognitive decline across studies

Consistent long-term safety

Consistent safety and tolerability profile in the long-term trial with no new safety signals observed

AXS-05 in Alzheimer's disease agitation: Key takeaways

Agitation is a ***highly prevalent and debilitating symptom*** of Alzheimer's disease that impacts up to 76% of patients

There is an ***urgent need*** for new and effective treatments with a favorable safety profile, with only one FDA-approved agent, an atypical antipsychotic

AXS-05 is a ***novel NMDA antagonist and sigma-1 agonist*** that targets key neurotransmitters implicated in Alzheimer's disease

AXS-05 demonstrated ***rapid and robust efficacy*** across three Phase 3, placebo-controlled trials

AXS-05 was ***not associated with*** death, cognitive decline, sedation, or increased risk of falls in short- and long-term trials

AXS-05

Sue Giordano, PhD

Senior Vice President, Medical Affairs

Smoking cessation

~34M adults in the U.S. smoke cigarettes, ~50% of whom live with a smoking-related disease[1]

Single ***largest cause of preventable disease*** and death in the U.S., accounting for nearly 1 in 5 deaths[1]

Associated with over ***$300 billion*** in annual costs in the U.S.[1]

1. U.S. Department of Health and Human Services 2020

Substantial health impacts of smoking

#1 cause of preventable mortality and morbidity globally[1]

3x higher all-cause mortality compared to non-smokers[1]

2/3 of deaths in current smokers are attributable to smoking[1]

10 years of life lost due to smoking[1]

Substantial health consequences of smoking include increased risk of developing[2]:

- Colorectal, liver, and lung cancer
- Cardiovascular disease
- Chronic obstructive pulmonary disease (COPD)
- Impaired immune function

1. Banks E, et al. *BMS Med.* 2015; 2. Surgeon General Report 2014

Unmet needs in the treatment of nicotine dependence

70% of smokers want to quit[1]

Only *3-5%* who attempt to quit without assistance are successful for 6-12 months[2]

Need for new and effective treatment options:

- Only *3* FDA-approved treatments, including NRT, bupropion, and varenicline
- *<20%* of smokers achieved sustained abstinent rates with pharmacological intervention at 12 months of treatment[3]

~40% of adult cigarette consumption is by individuals with psychiatric conditions[4]

1. Hughes JR, et al. *Addiction* 2004; 2. Banks E, et al. *BMS Med.* 2015; 3. Cahil K, et al. *Cochrane Database Syst Rev.* 2013; 4. National Survey on Drug Use and Health. SAMHSA 2013

Rationale for AXS-05 in smoking cessation

Alterations in NMDA mediated signaling have been implicated in the neurobiology of nicotine dependence. Nicotine acts on α4β2 nicotinic cholinergic receptors in the mesolimbic dopamine pathway[1-6]

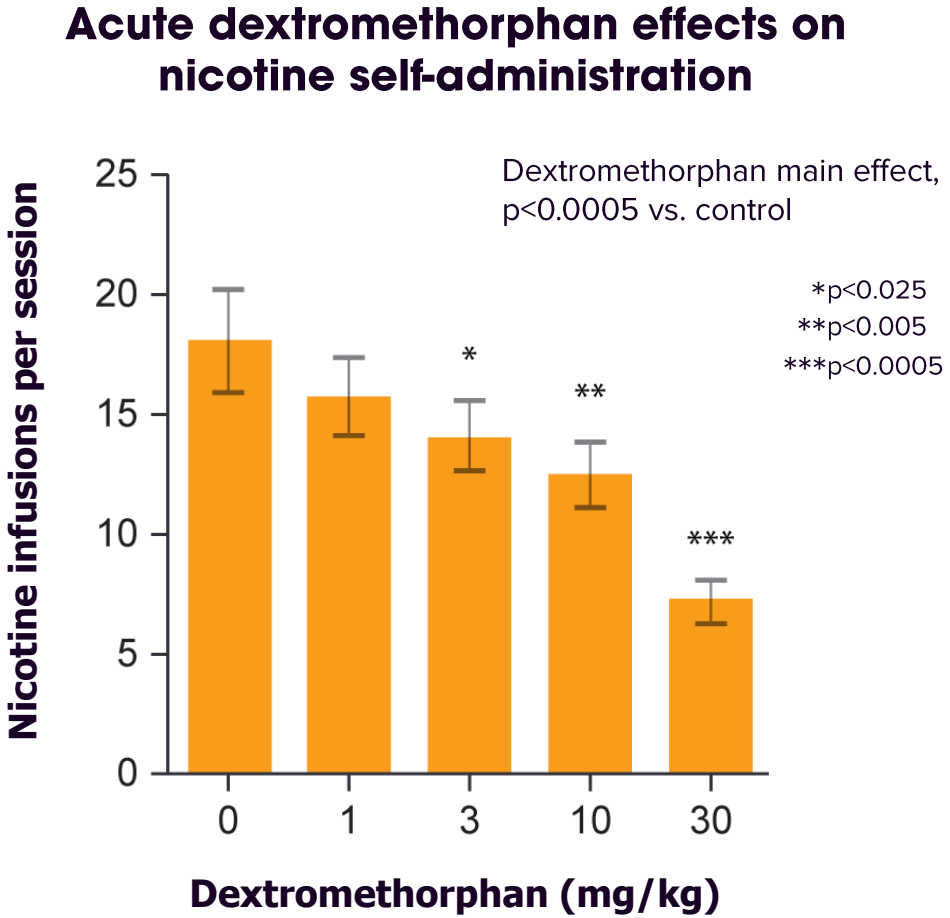
Dextromethorphan in addition to modulating NMDA and sigma-1 is also an antagonist of α3β4, α4β2, and α7 nicotinic receptors[7]

Dextromethorphan has been shown to *reduce nicotine self-administration* in rats[8,9]

Bupropion in addition to being a dopamine and norepinephrine reuptake inhibitor is also an antagonist of α3β2, α4β2, and α7 nicotinic receptors[10]

1. Li X, et al. *Neuropharmacology* 2014; 2. D'Souza MS. *Frontiers in Neuroscience* 2015; 3. Kosowski AR, et al. *Psychopharmacology (Berl)* 2004; 4. Kenny PJ, et al. *Neuropsychopharmacology* 2009; 5. Mao D, et al. *Journal of Neuroscience* 2011; 6. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press; 2013. 7. Hernandez SC, et al. *J Pharmacol Exp Ther.* 2000; 8. Glick SD, et al. *Eur J Pharmacol.* 2001; 9. Briggs SA, et al. *Pharmacol Biochem Behav.* 2016; 10. Slemmer JE, et al. *J Pharmacol Exp Ther.* 2000

Dextromethorphan reduces nicotine administration in nicotine dependent rats[1]



DM showed a significant and dose-dependent decrease in nicotine self-administration in nicotine dependent rates

Effects were significant at 3 mg/kg and most effect at 30 mg/kg

Because humans are extensive DM metabolizers, translating to these findings to humans necessitates metabolic inhibition

1. Briggs SA, et al. *Pharmacol Biochem Behav.* 2016

AXS-05 in smoking cessation: Key takeaways

Smoking remains highly prevalent and is the ***leading cause*** of preventable morbidity and mortality globally

Most smokers want to quit, but there is a significant gap in effective and well-tolerated FDA-approved treatments

AXS-05 is a promising investigational therapy for smoking cessation, supported by mechanistic rationale and pre-clinical and early clinical data

Solriamfetol

Andrew Cutler, MD

Clinical Associate Professor of Psychiatry

SUNY Upstate Medical University

axsome

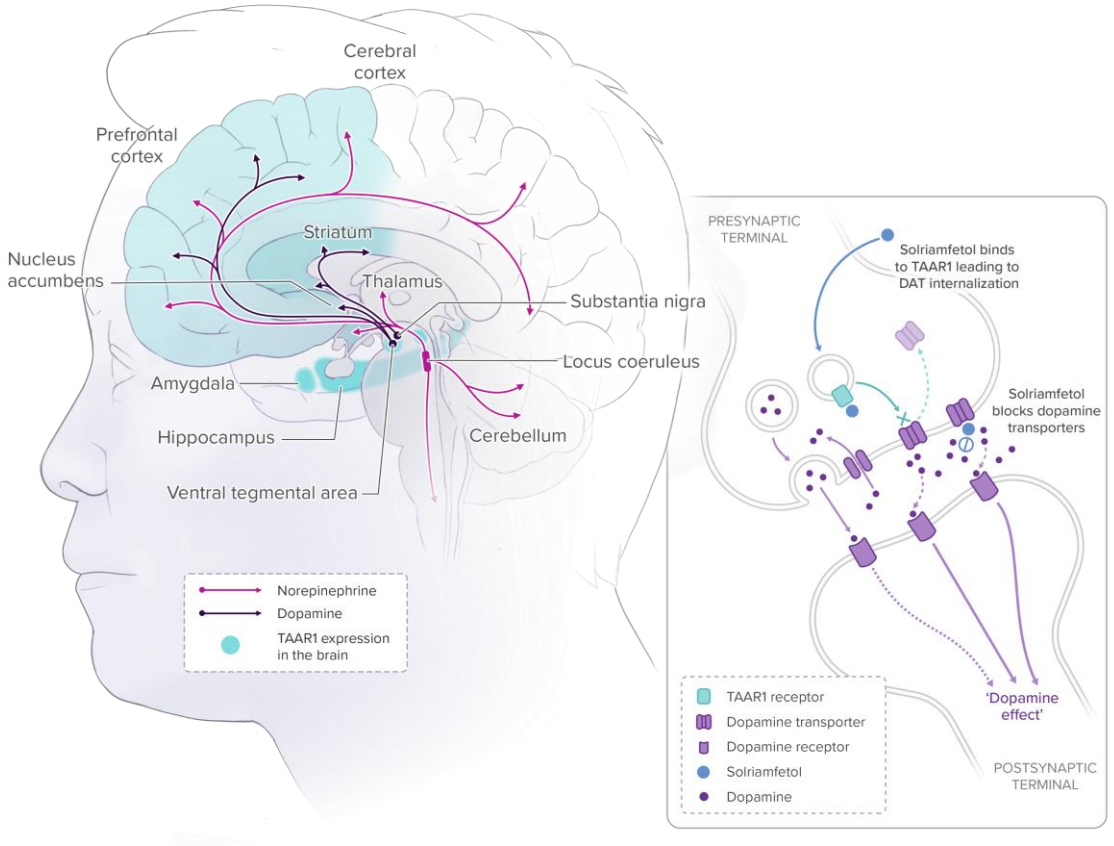
ADVANCING FRONTIERS IN BRAIN HEALTH: Novel MOA, novel targeted indications

Unique pharmacology of solriamfetol supports potential utility in a broad range of CNS conditions

Solriamfetol was initially developed as a dopamine and norepinephrine reuptake inhibitor (DNRI) with *wake-promoting effects*

Preclinical and clinical evidence[1,2] suggest TAAR1 plays a role in neuropsychiatric conditions related to the *dysregulation of monoaminergic transmission*

Multimodal activity of solriamfetol *selectively inhibits* the reuptake of dopamine and norepinephrine and exhibits *agonist activity* at TAAR1 receptors in the brain



1. Raony I, et al. *Prog Neuropsychopharmacol Biol Psychiatry* 2022; 2. Halff EF, et al. *Trends Neurosci.* 2023

Attention deficit hyperactivity disorder (ADHD)

Chronic neurobiological and developmental disorder affecting an estimated ~***22M*** people in the U.S.[1], including ~7M children aged 3-17 years old[2]

Characterized by a persistent pattern of inattention and/or hyperactive-impulsive behaviors[3]

Associated with significant impairment in social, academic, and occupational functioning and development[3]

1. Facts About ADHD in Adults. CDC 2024; 2. Data and Statistics on ADHD. CDC 2024; 3. Attention-Deficit/Hyperactivity Disorder. NIMH 2024

Significant burden of ADHD on psychosocial functioning and overall quality of life

ADHD in adolescents and adults is associated with:

Increased risk of premature mortality[1]

Higher rates of natural/unnatural causes of death linked to psychiatric comorbidities[2]

Increased likelihood of getting arrested[3]

Lower likelihood of obtaining a high school/college degree or being employed full-time[3]

Greater difficulty maintaining relationships[4]

More likely to have been treated for a sexually transmitted disease[4]

Increased risk of motor vehicle accidents[5]

1. O'Nions E, et al. *Br J Psychiatry* 2025; 2. Sun S, et al. *JAMA Psychiatry* 2019; 3. Biederman J, et al. *J Clin Psychiatry* 2006; 4. Barkley RA, et al. *J Am Acad Child Adolesc Psychiatry* 2006; 5. Barkley RA, et al. *Pediatrics* 1996

ADHD is often underdiagnosed and undertreated

>90% of patients diagnosed with ADHD in childhood continue to exhibit symptoms into adulthood[1]

An estimated >80% of adults with ADHD are not diagnosed and/or treated for their ADHD due to lack of awareness and accompanying psychiatric comorbidities[2]

Untreated ADHD leads to poor clinical and functional outcomes[2]

1. Sibley MH, et al. *Am J Psychiatry* 2022. 2006; 2. Ginsberg Y, et al. *Prim Care Companion CNS Disord.* 2014

ADHD often presents with and increases risk of developing other psychiatric disorders

Adult ADHD is associated with increased risk of developing other psychiatric disorders[1]

3x more likely to develop major depressive disorder

4x more likely to develop any mood disorder

2x more likely to experience substance abuse/dependence

Prevalence of comorbid psychiatric disorders in adults with ADHD[2]

Up to 55%	Any depressive disorder	***Up to 80%***	Any bipolar disorder
Up to 84%	Any anxiety disorder	***Up to 72%***	Any substance use disorder

1. Mattingly G. and Childress A, *J Clin Psychiatry* 2024; 2. Choi W, et al. *PLoS One* 2022

ADHD treatment landscape and unmet need

Stimulants

Dopamine-norepinephrine modulators

- Methylphenidates
- Amphetamines

IR/LR, tablet, chewable, liquid, patch

Nonstimulants

Norepinephrine modulators

- Atomoxetine
- Viloxazine

Alpha2 agonists

- Clonidine
- Guanfacine

Off-label medications

- Bupropion
- Modafinil
- Desipramine
- Memantine
- Solriamfetol

Limitations of currently available treatment options:

Stimulants

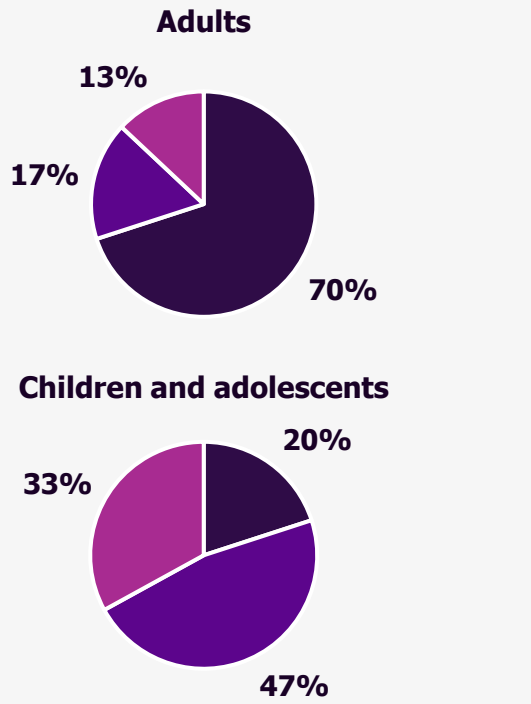
- Schedule II controlled substances
- Abuse/misuse potential
- Cardiovascular effects
- Sleep disturbances
- Irritability
- Rebound symptoms
- Weight changes
- Loss of appetite

Non-stimulants

- Slower onset of action
- Modest efficacy
- GI side effects
- Sedative effects

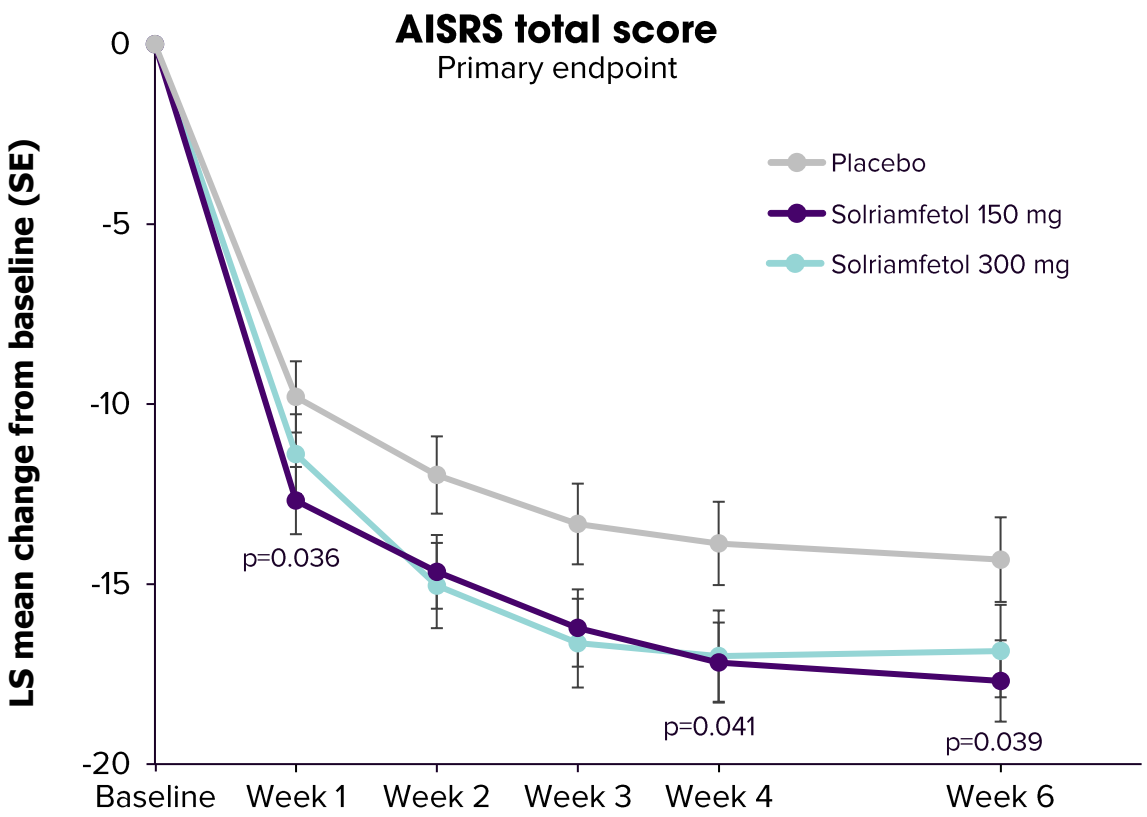
Approximately ***30%*** of ADHD patients have an inadequate response to stimulant therapy or experience intolerable side effects[2,3]

Current treatments



Symphony Metys FY 2024 TRx

Significant improvements in ADHD symptoms with solriamfetol treatment in FOCUS Phase 3 trial in adult patients



Substantial improvement in ADHD symptoms observed as early as Week 1 (p=0.036, solriamfetol 150 mg)

Mean reduction in AISRS at Week 6 of 17.7 points represents a *45% improvement* from baseline in ADHD symptoms (solriamfetol 150 mg)

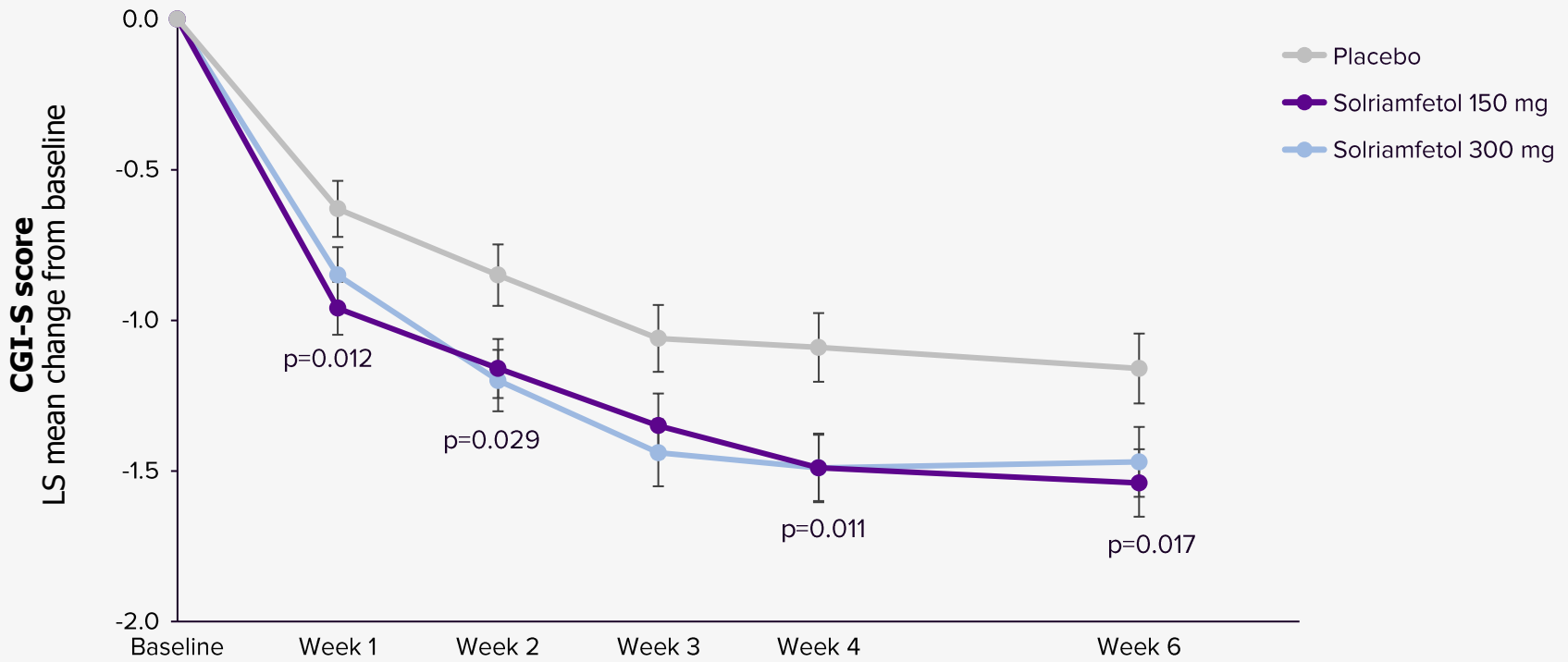
Significantly greater percentage of patients achieved a clinical response (≥30% reduction in AISRS) vs. placebo (p=0.024, solriamfetol 150 mg)

Well tolerated with a side effect profile *consistent* with the established safety profile of solriamfetol

1. p-values shown for solriamfetol 150 mg dose vs. placebo only (primary analysis)

Improvements in overall ADHD disease severity with solriamfetol

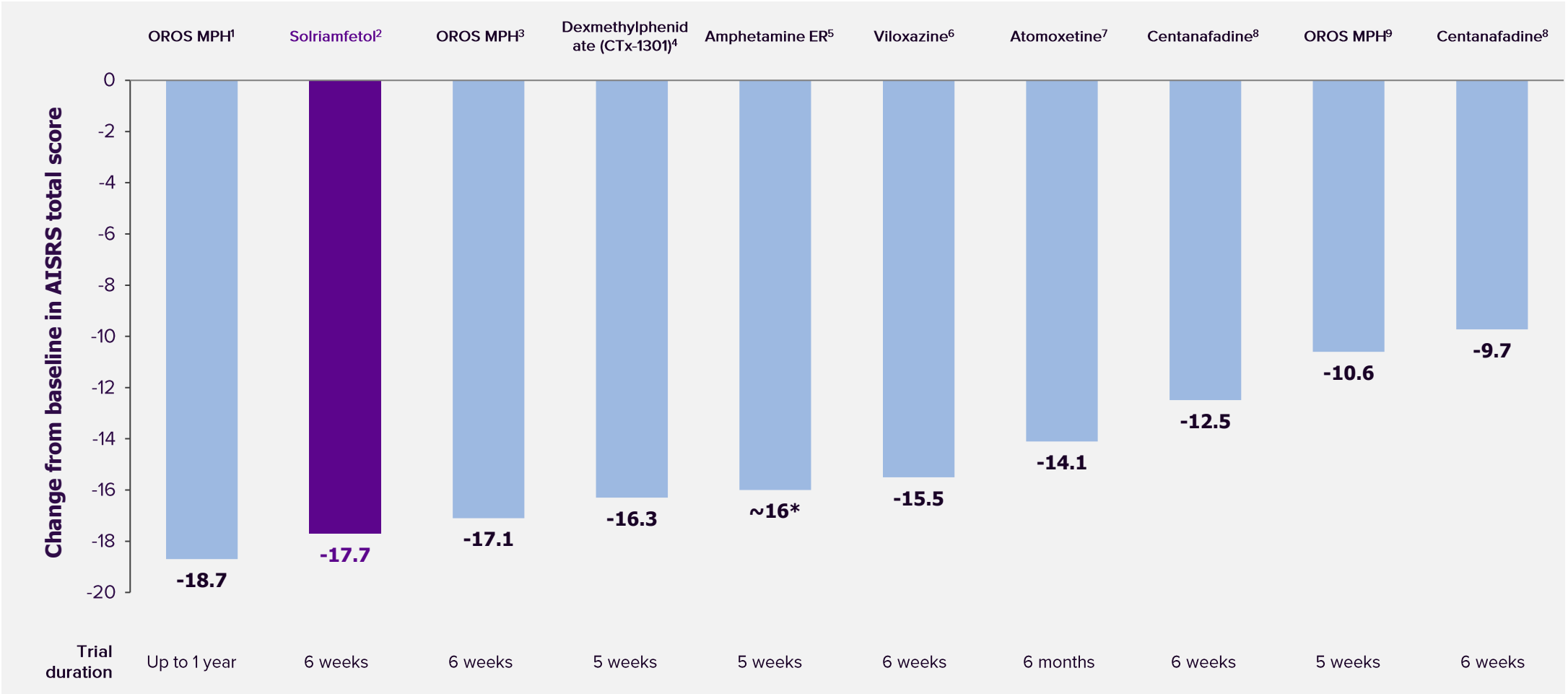
FOCUS[1]



Improvements in severity of overall ADHD as measured by the CGI-S total score starting as early as Week 1 (p=0.012)

1. p-values shown for solriamfetol 150 mg dose vs. placebo only (primary analysis)

Reported AISRS total score reductions from baseline for approved and investigational ADHD pharmacotherapies



Not a head-to-head comparison. Data are from separate studies.

1. Adler LA, et al. *J Clin Psychopharmacol.* 2011; 2. Axsome Therapeutics, Inc. Data on file; 3. Goodman DW, et al. *J Clin Psychiatry* 2017; 4. Cingulate Inc. Press Release, July 11, 2023; 5. Cuter AJ, et al. *J Clin Psychiatry* 2022; 6. QELBREE [Prescribing Information]. Supernus Pharmaceuticals, Inc. Revised January 2025; 7. Spencer TJ, et al. *J Atten Disord.* 2010; 8. Adler LA, et al. *J Clin Psychopharmacol.* 2022; 9. Adler LA, et al. *J Clin Psychopharmacol.* 2009

Solriamfetol in ADHD: Key takeaways

ADHD is a *chronic and neurobiological developmental disorder* that poses a significant burden on patients

Many patients experience an *inadequate response or tolerability issues* with currently available treatments

Solriamfetol is a *novel DNRI* with TAAR1 agonist activity that targets key neurotransmitter pathways in the brain implicated in ADHD

Solriamfetol demonstrated *substantial and statistically significant improvements* in ADHD symptoms in a Phase 3 trial in adult patients

Solriamfetol was *well tolerated* in the trial, with a safety profile that was consistent with the established safety profile of solriamfetol

Major depressive disorder (MDD)

— ~2/3 of patients experience inadequate response to first-line treatment[3]

One of the most common mental disorders in the U.S., impacting ***~21M*** adults each year[1,2]

Serious and ***chronic mental health*** condition causing persistently low or depressed mood and a loss of interest or pleasure in daily activities, and may impair one's sleep, appetite, ability to concentrate, and/or self-worth[1]

1. Major Depression. *NIMH* 2023; 2. Hasin DS, et al. *JAMA Psychiatry* 2018; 3. Rush AJ, et al. *Am J Psychiatry* 2006

MDD with EDS is a prevalent and underserved subgroup of depression

~50% of patients with MDD have concomitant excessive daytime sleepiness (EDS)[1]

	Incident EDS	
	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
R^2	0.06	0.13
Male	-	2.0 (1.2-3.3)**
Non-Caucasian	-	2.8 (1.4-5.4)**
Age ≤ 30 years	-	4.2 (2.3-7.8)**
Age ≥ 65 years	-	2.2 (1.3-3.8)**
Allergy/asthma	1.5 (1.0-2.4)†	1.6 (1.0-2.6)*
Diabetes	1.7 (1.0-3.0)*	1.4 (0.8-2.5)
Hypertension	1.1 (0.7-1.8)	-
Migraine	1.2 (0.7-2.2)	-
Obesity	1.8 (1.2-2.8)**	2.0 (1.2-3.2)**
Sleep apnea	1.7 (0.8-3.7)	-
Depression	2.6 (1.6-4.2)**	3.1 (1.8-5.2)**

Model 1 = multivariable backward conditional model of clinical risk factors. Model 2 = model 1 plus forced entry of sociodemographic factors. OR, odds ratio; 95% CI, 95% confidence interval. † P < 0.10, * P < 0.05, ** P < 0.01

Papakostas GI, et al. *Biol Psychiatry* 2006

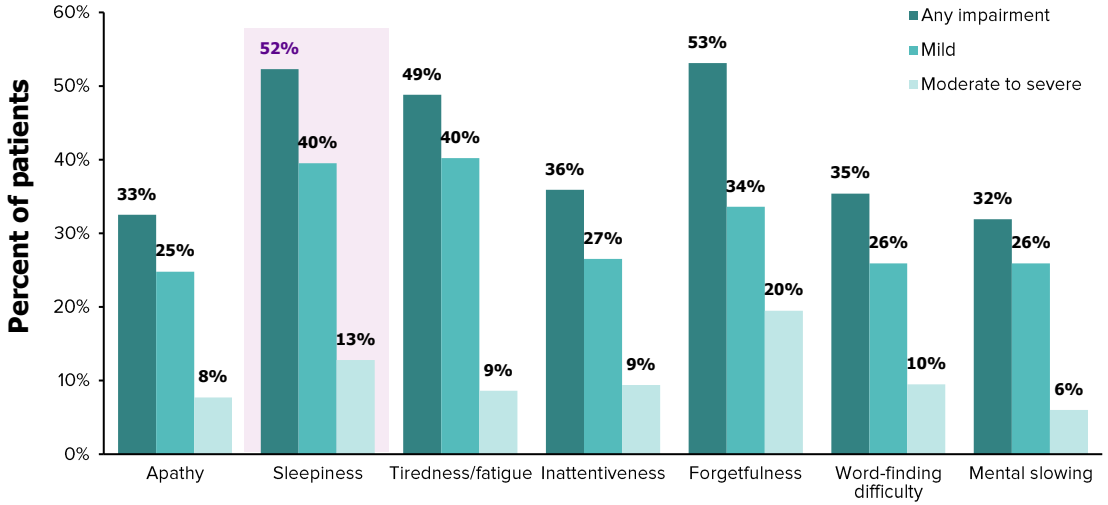
- In a large longitudinal study of 1,395 adults[2], a lifetime history of depression was associated with a *significantly increased risk* of developing EDS over a 7.5-year follow-up
  - Depression was the single strongest predictor of EDS onset and independent of other factors such as sleep apnea and obesity
- Severity of depression has also been *linked to* higher rates of EDS[3,4]
- There are *no FDA-approved therapeutics* specifically for treating MDD with EDS

1. Hein M, et al. *J Affect Disord.* 2019; 2. Papakostas GI, et al. *Biol Psychiatry* 2006; 3. Chellappa SL and Araujo JF. *Braz J Psychiatry* 2006; 4. Mume CO. *Libyan J Med* 2010

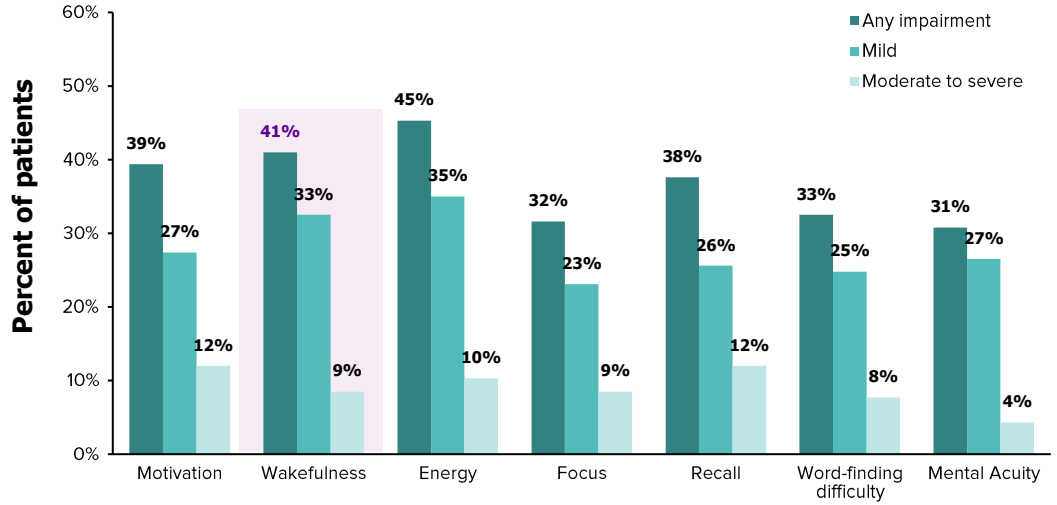
EDS is frequently reported by MDD patients who have responded to antidepressant treatment

In a cross-sectional study of 117 MDD patients, ***sleepiness and impairment*** in wakefulness and energy were common symptoms in patients who responded to their antidepressant therapy across different self-rated measures[1]

Responders with cognitive and physical impairment
Study-specific questionnaire



Responders with cognitive and physical impairment
Cognitive and physical functioning questionnaire



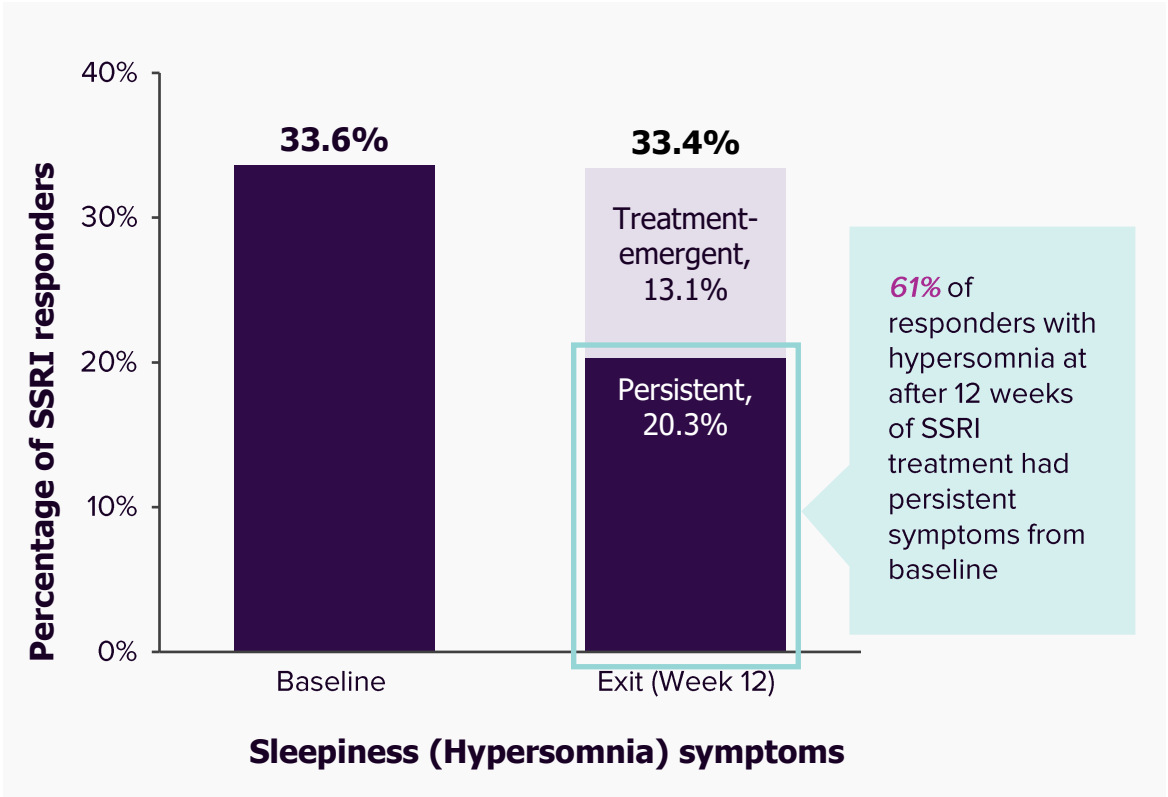
Significant sleepiness as measured by the ESS was reported in ***>40%*** of responders

ESS = Epworth Sleepiness Scale; CPFQ = Cognitive and Physical Functioning Questionnaire

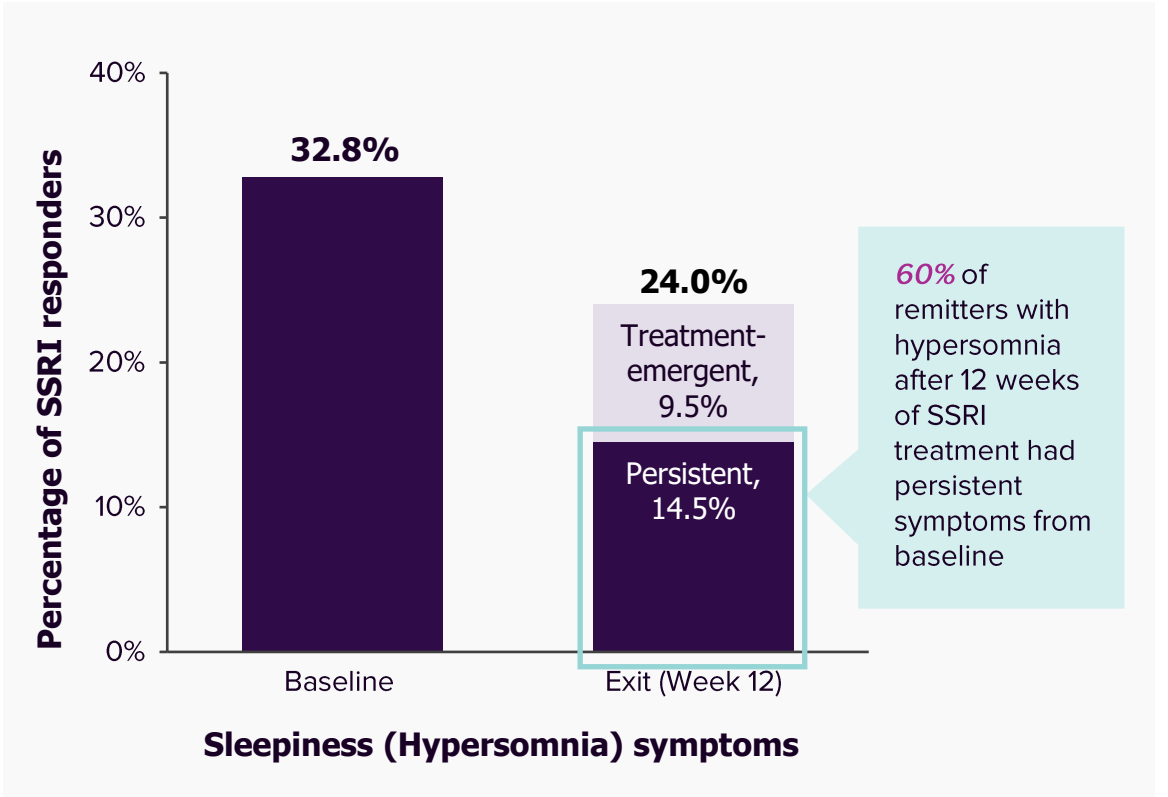
1. Fava, M. et al. J Clin Psychiatry (2006).

Excessive sleepiness is a common residual symptom in MDD patients who respond or remit after antidepressant therapy

Sleepiness symptoms before and after SSRI treatment in patients who responded but did not remit by Week 12[1]
(N=428)



Sleepiness symptoms before and after SSRI treatment in patients who remitted by Week 12[2]
(N=943)



1. McClintock SM, et al. *J Clin Psychopharmacol.* 2013; 2. Nierenberg AA, et al. *Psychol Med.* 2009

EDS has been linked to poor clinical outcomes in MDD

In a cross-sectional study of 252 patients with MDD[1]:

- MDD patients with hypersomnolence were found to have *greater depression* ratings and *higher rates* of suicidal ideation
  - Hypersomnolence was an independent risk factor associated with a *3-fold increase* in the risk of depression non-remission (p=0.034)

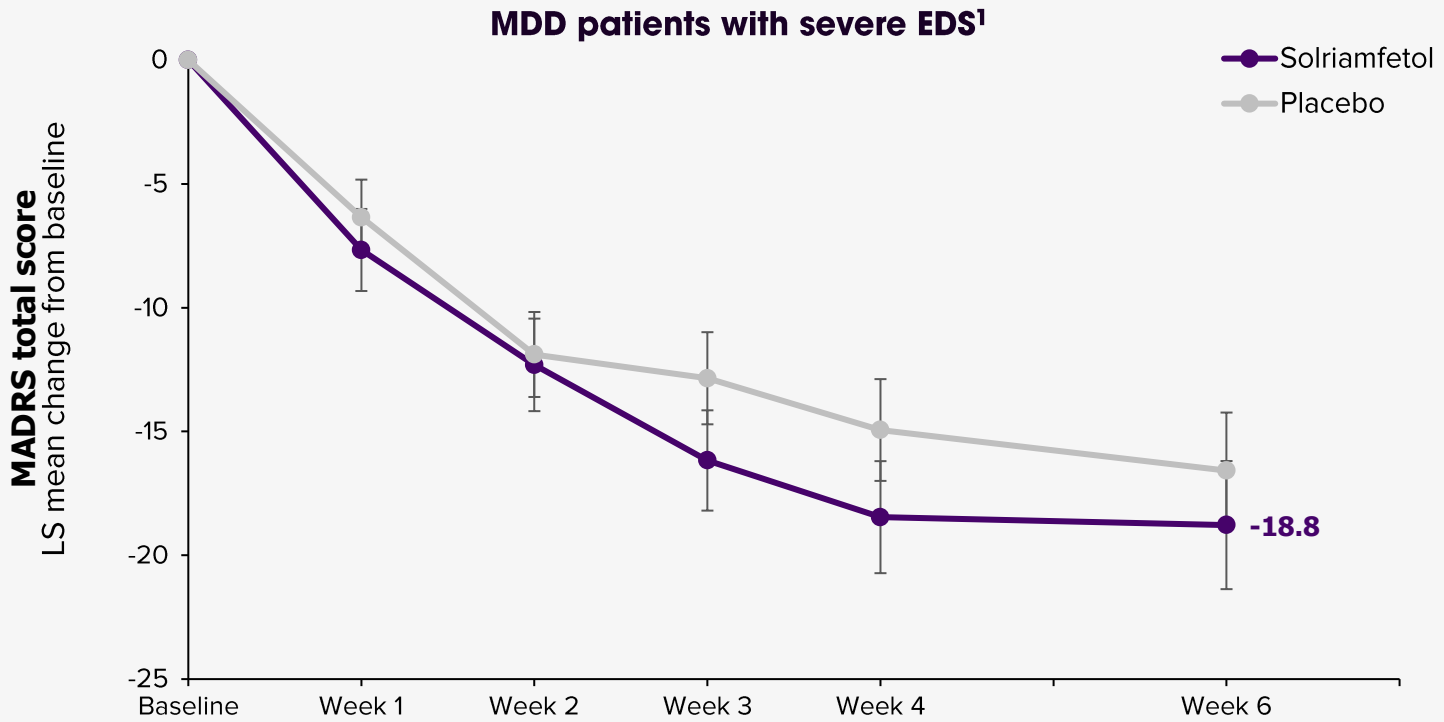
In a cross-sectional study of 70 patients with MDD[2]:

- Patients with higher levels of EDS had *significantly greater risk* of suicidal ideation, more severe depression, and experienced a *longer duration* of their depressive episode

1. Cheung MMS, et al. *Sleep Medicine* 2024; 2. Chellappa SL and Araujo JF. *Braz J Psychiatry* 2006

Early clinical evidence supports continued development of solriamfetol in MDD with EDS

PARADIGM

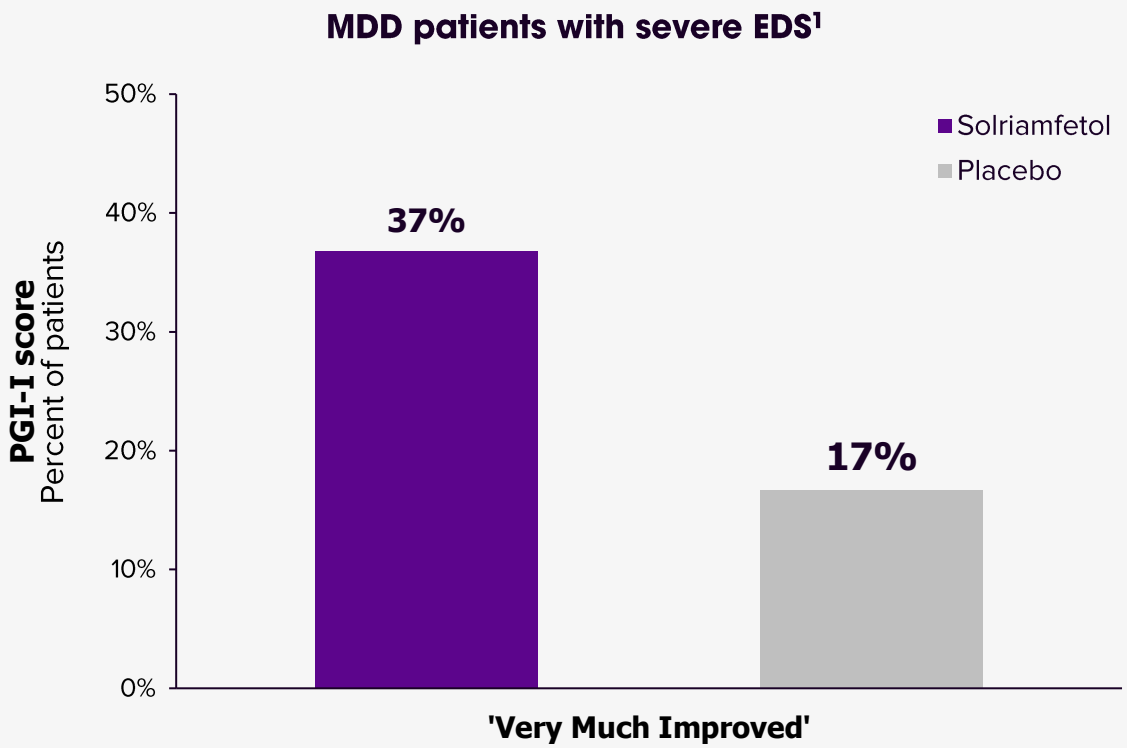


Substantial improvements in the depressive symptoms as measured by the MADRS total score compared to placebo in MDD with severe EDS subgroup

1. Prespecified subgroup (n=51, severe EDS defined as ESS score ≥16)

Improvements in overall depression severity in MDD patients with severe EDS

PARADIGM



>2x as many patients reported being ‘Very Much Improved’ in overall depression severity as measured by the PGI-I score compared to placebo in MDD with severe EDS subgroup

1. Prespecified subgroup (n=51, severe EDS defined as ESS score ≥16)

Solriamfetol in MDD with EDS: Key takeaways

Approximately 50% of patients with MDD have concomitant excessive daytime sleepiness (EDS)

MDD with EDS is associated with poor clinical outcomes for patients with depression

Early clinical evidence supports continued development of solriamfetol in MDD with EDS

Solriamfetol has the potential to be the first approved treatment for MDD with EDS

Shift work disorder (SWD)

~15 million U.S. workers may suffer from SWD

10-43% have SWD[1,3]

Approximately *1 in 3 people* working in the U.S. work an alternate shift[2]

Shift work disorder (SWD) is a combination of excessive sleepiness during wakefulness and persistent insomnia during daytime sleep when working outside a 7 a.m. to 6 p.m. workday[1]

Shift work has long been associated with multiple serious health complaints and a 23% greater risk of sustaining a work-related injury[4-5]

No new medications approved since 2007, and considerable residual sleepiness reported when medication is used[6]

1. Sateia MJ. *Chest* 2014; 2. Alterman T, et al. *Am J Ind Med.* 2013; 3. Wickwire EM. *Chest* 2017; 4. Smith L, et al. *Lancet* 1994; 5. Akerstedt T & Wright KP. *Sleep Med Clin.* 2009; 6. Czeisler CA, et al. *N Engl J Med.* 2005

Solriamfetol

Susan McElroy, MD

Professor of Psychiatry & Behavioral Neuroscience |
Chief Research Officer and Director of
Psychopharmacology Research, Lindner Center of HOPE

| *University of Cincinnati*

axsome

ADVANCING FRONTIERS IN BINGE EATING DISORDER: Novel MOA, novel indication

Binge eating disorder (BED)

>7 million people in the U.S. have BED[1]

BED is *1.75x more common* in women than in men[1]

Binge eating disorder (BED) is the most common eating disorder, affecting 2.8% of adults and 1.6% of adolescents in the US[1,2]

BED is thought to involve issues with food reward processing, impulse control, cognitive control, and appetite regulation[1,3]

Unmet medical need associated with a 2- to 3-fold increased risk of psychiatric and medical comorbidities[4]

1. Hudson JI, et al. *Biol Psychiatry* 2007; 2. Swanson SA, et al. *Arch Gen Psychiatry* 2011; 3. Kessler RM, et al. *Neurosci Biobehav Rev.* 2016; 4. McElroy SL, et al. *J Clin Psychiatry* 2020;

Recent formal recognition of BED in DSM-5 diagnostic criteria

DSM-5 criteria for BED

Recurrent episodes of binge eating

- Characterized by:
  - Eating a larger amount of food than normal during a short time frame (any 2-hour period)
  - A sense of lack of control overeating during the episode
- Occurs on average at least once a week for 3 months

Associated behaviors and emotional responses

- Associated with at ≥3 of the following:
  - Eating much more rapidly than normal
  - Eating until feeling uncomfortably full
  - Eating large amounts of food when not feeling physically hungry
  - Eating alone because of feeling embarrassed by how much one is eating
  - Feeling disgusted with oneself, depressed, or very guilty afterward

Additional characteristics

- Marked distress regarding binge eating is also present
- Binge eating is not associated with recurrent use of inappropriate compensatory behavior such as purging, excessive, exercise, etc.
- Binge eating does not occur exclusively during the course of bulimia nervosa or anorexia nervosa

Source: APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (2013)

Substantial burden of BED on patient outcomes

BED in adolescents and adults is associated with:

Functional impairment at work/school, social life and leisure activities, and family life/home responsibilities[1,2]

Reduced mental and physical health-related quality of life[3-9]

Increased medical morbidity, including cardiovascular problems, metabolic syndrome, and type 2 diabetes[10-15]

Higher rates of comorbid psychiatric symptoms, including mood and anxiety disorders[10,13,16-19]

Increased risk for developing psychiatric symptoms[20]

Higher prevalence among people with obesity[21]

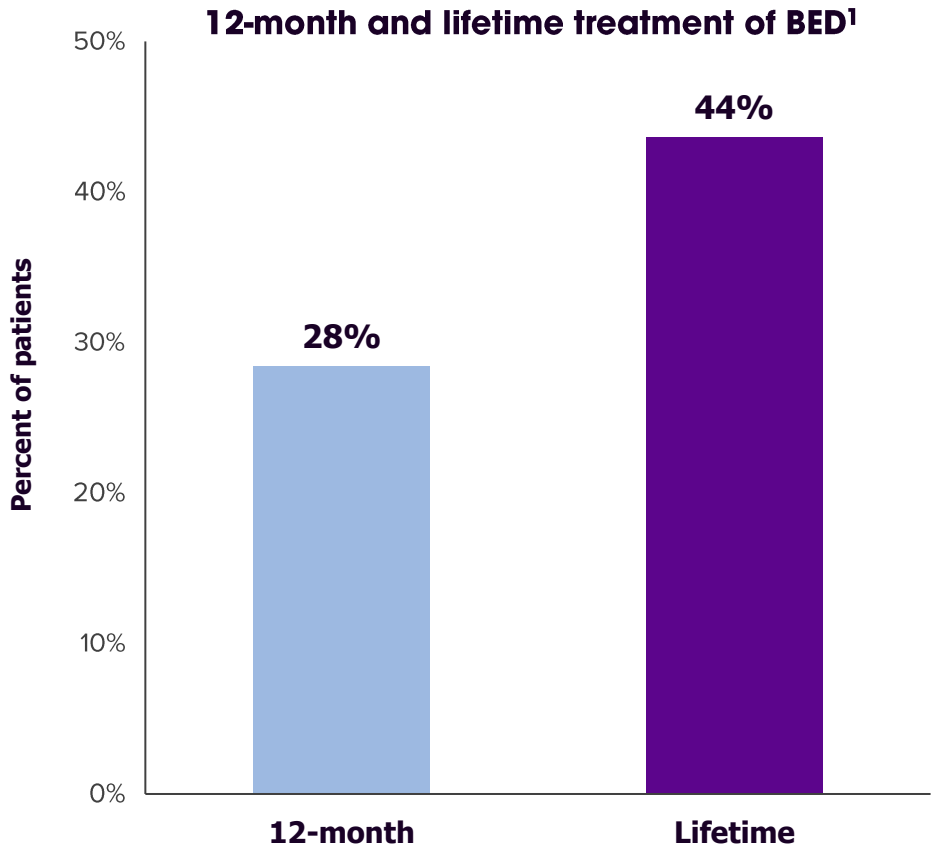
Greater healthcare utilization[1]

1. Hudson JI, et al. *Biol Psychiatry* 2008; 2. Kessler RC, et al. *Epidemiol Psychiatr Sci.* 2014; Grenon R, et al. *Womens Health Issues* 2010; Latner JD, et al. *J Clin Psychol Med Settings* 2008; Masheb RM and Grilo CM. *Eat Weight Disord.* 2004; Perez M and Warren CS. *Obesity (Silver Spring)* 2012; Rieger E, et al. *Int J Eat Disord.* 2005; Sandberg RM, et al. *J Obes.* 2013; Vancampfort D, et al. *Psychiatry Res.* 2014; Friederich HC, et al. *Int J Obes (Lond)* 2006; Hudson JI, et al. *Am J Clin Nutr.* 2010; Webb JB, et al. *Eat Behav.* 2011; Guerdjikova AI, et al. *Eat Weight Disord.* 2007; Roehrig M, et al. *Obesity (Silver Spring)* 2009; Barnes RD, et al. *Prim Care Companion CNS Disord.* 2011; Fandino J, et al. *Compr Psychiatry* 2010; Grilo CM, et al. *Int J Eat Disord.* 2009; Javaras KN, et al. *J Clin Psychiatry.* 2008; Jones-Corneille LR, et al. *Obes Surv.* 2012; Grucza RA, et al. *Compr Psychiatry* 2007; Smith DE, et al. *Ann Behav Med.* 1998.

Significant need for new treatment options for people living with BED

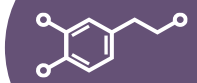
- >70% of patients with BED don't receive treatment in the prior 12 months[1]
- Standard of care for BED is not yet clearly defined[2]
- Individuals with BED may be reluctant to seek treatment due to shame, embarrassment, and a lack of awareness of the disorder[3]
- Proper diagnosis and treatment remains a challenge for physicians due to insufficient awareness of its recent diagnostic criteria and limited available treatment options[3]

BED is a highly underserved psychiatric disorder with only one FDA-approved treatment



1. Hudson JI, et al. *Biol Psychiatry* 2008; 2. McElroy SL, et al. *Ther Clin Risk Manag.* 2012; 3. Korstein SG, et al. *Prim Care Companion CNS Disord.* 2016

Rationale for solriamfetol in BED



Solriamfetol inhibits the reuptake of dopamine and norepinephrine, neurotransmitters implicated in the pathophysiology of binge eating disorder[1-3]

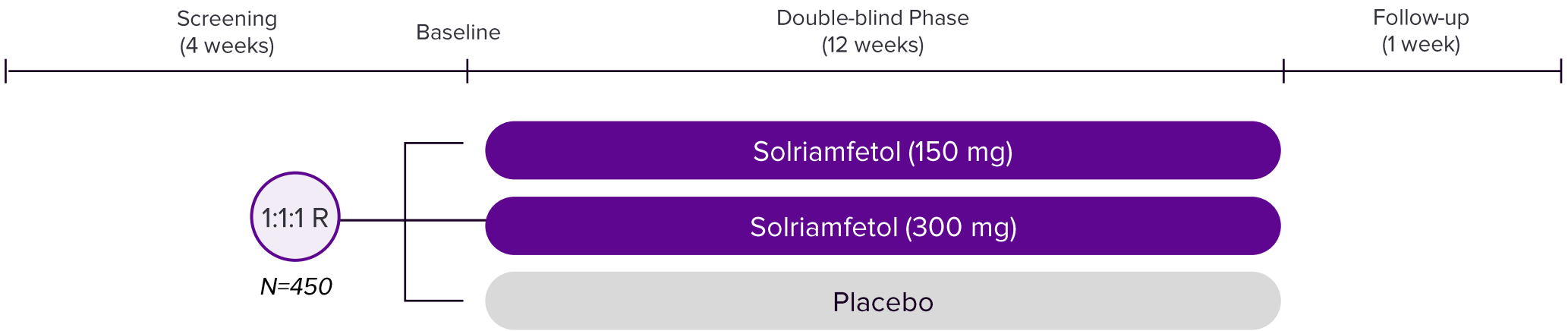
Pre-clinical and clinical data support potential effects of solriamfetol on appetite, food consumption, and weight[4,5]

Link between narcolepsy and BED

1. Giel KE, et al. *Nat Rev Dis Primer* 2022; 2. Bello NT and Hajnal A. *Pharmacol Biochem Behav.* 2010; 3. Pruccoli J, et al. *Int J Mol Sci.* 2021; 4. Malhotra A, et al. *Sleep Med.* 2022; 5. SUNOSI [Prescribing Information]. Axsome Therapeutics, Inc. New York, NY.

Ongoing Phase 3 trial of solriamfetol in patients with BED

ENGAGE Phase 3 Trial



Key eligibility criteria

- 18-55 years of age with diagnosis of BED (DSM-5)

Primary endpoint

- Change from baseline in days with binge eating episodes

Solriamfetol in BED: Key takeaways

Despite being the most common eating disorder, BED remains significantly *underrecognized, underdiagnosed, and undertreated*

There is an *urgent need for a new pharmacologic approach* for BED, with currently only one FDA-approved agent

BED is associated with high rates of *psychiatric comorbidities*, which may worsen with inadequate treatment

Solriamfetol has the potential to be an *important new treatment option* for this underserved patient population

AXS-12

Michael Thorpy, MD

Professor of Neurology | Director of Sleep-Wake Disorders Center, Montefiore Medical Center

| *Albert Einstein College of Medicine*

axsome

ADVANCING FRONTIERS IN NARCOLEPSY: Novel MOA addressing critical gaps in care

AXS-12 (reboxetine)

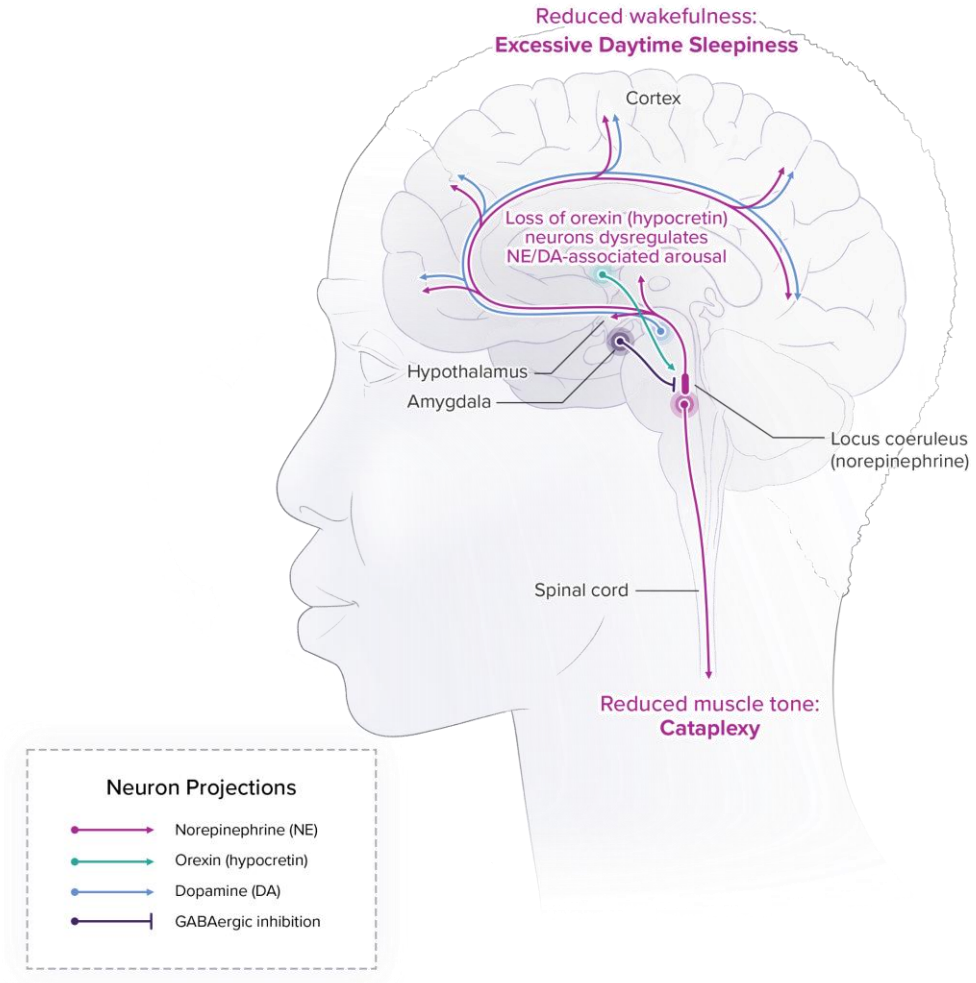
Novel pharmacological approach for the treatment of narcolepsy

Norepinephrine and dopamine play *important roles* in sleep-wake regulation (both) and in maintaining muscle tone during wakefulness (norepinephrine)[1-3]

The loss of orexin input *inhibits the production* of these neurotransmitters[1,2]

- Decreased norepinephrine signaling is thought to contribute to cataplexy, EDS, and cognitive impairment[1,4-7]
- Decreased dopamine signaling is thought to contribute to EDS and cognitive impairment[1,4]

AXS-12 *inhibits the reuptake* of both neurotransmitters, improving both norepinephrine and cortical dopamine signaling in the brain



1. Szabo ST, et al. *Sleep Med Rev.* 2019; 2. Krahn LE, Zee PC, & Thorpy MJ. *Adv Ther.* 2022; 3. Scammell TE. *N Engl J Med.* 2015; 4. Stahl SM & Grady MM. *J Clin Psychiatry* 2003; 5. Burgess CR & Peever JH. *Curr Biol.* 2013; 6. Wu MF, et al. *Neuroscience* 1999; 7. Bruinstroop E, et al. *J Comp Neurol.* 2012

Narcolepsy

Rare and debilitating neurological condition that affects approximately ***185,000*** people in the U.S.[1]

Characterized by cataplexy, excessive daytime sleepiness (EDS), hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep.[2-4]

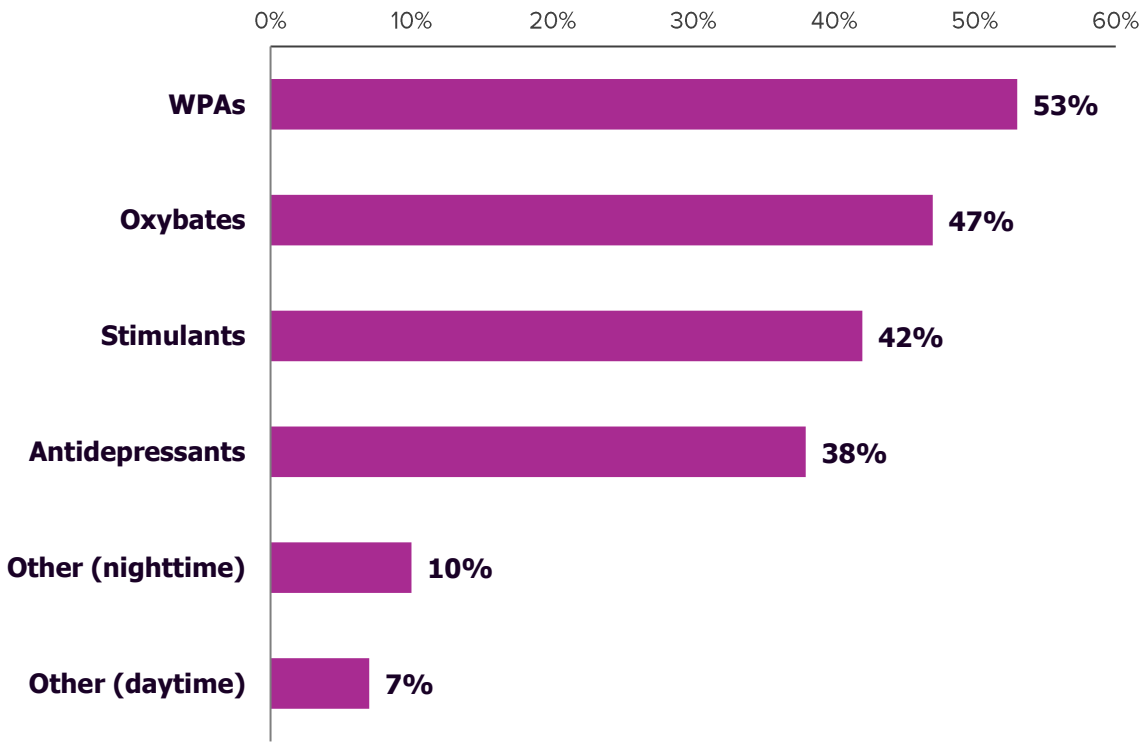
Up to ***70%*** of patients suffer from cataplexy, or the sudden reduction or loss of muscle tone while awake.[5]

1. “About Narcolepsy.” Narcolepsy Network 2024; 2. Sateia MJ. *Chest* 2014; 3. “Narcolepsy.” *NINDS* 2024; 4. España RA & Scammell TE. *Sleep* 2011; 5. Swick TJ. *Nat Sci Sleep* 2015

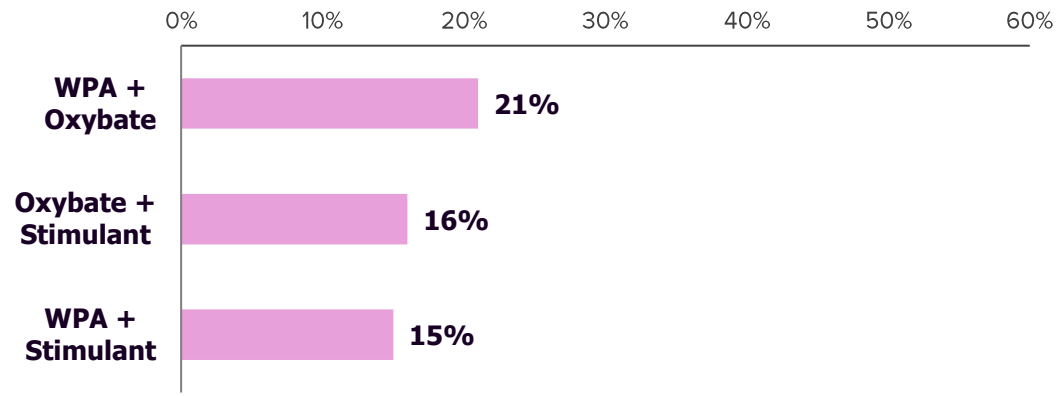
Narcolepsy type 1 treatment landscape

Results from the CRESCENDO Survey (N=203)

Current treatments used by participants to treat their narcolepsy symptoms



Most common concurrently used treatments



30% reported taking 2+ classes of medication

31% reported taking 3+ classes of medication

Wake promoting agents (WPAs): armodafinil, modafinil, pitolisant, and solriamfetol; Oxybates: sodium oxybate and mixed salt oxybate; Stimulants: methylphenidate, amphetamines, others; Antidepressants: SSRIs, SNRIs, NDRI, tricyclics; Other nighttime medications: zolpidem, trazodone, pramipexole and others; Other daytime medications: lamotrigine, triamterene, levothyroxine and others; NT1 = narcolepsy type 1; Axsome Therapeutics, Inc. Data on file.

Unmet need for new treatment options in narcolepsy

Results from the CRESCENDO Survey

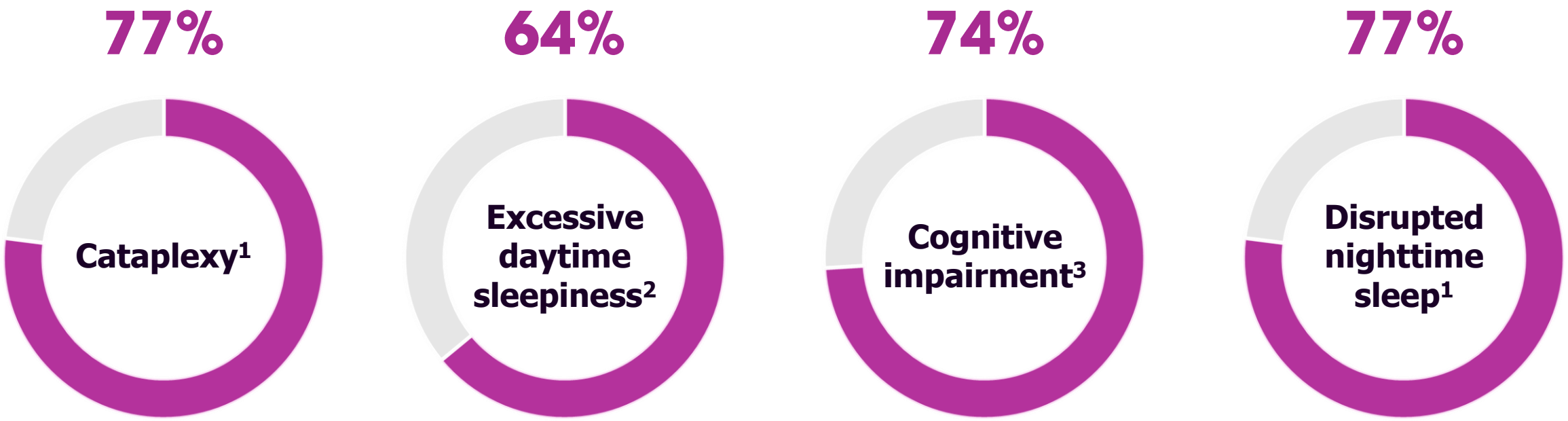
93%	of patients reported discontinuing at least one medication due to:
51%	Inadequate efficacy
42%	Burdensome side effects
34%	Recommendation by HCP to switch

Axsome Therapeutics, Inc. Data on file.

Inadequate relief of core narcolepsy symptoms despite treatment

Results from the CRESCENDO Survey

Percent of patients with persistent symptoms while on treatment



1. Self-reported; 2. Defined as Epworth Sleepiness Scale (ESS) score >10; 3. Defined as British Columbia Cognitive Complaints Inventory (BC-CCI) score >4
Axsome Therapeutics, Inc. Data on file.

Cataplexy can have a profound impact on all aspects of patients' lives[1]

CRESCENDO Survey. Patients who reported 'Agree/Extremely Agree' for each category.

AXS-12 clinical development program

CONCERT	SYMPHONY	ENCORE
Phase 2 (N=21)	*Phase 3 (N=90)*	*Phase 3 (OLP N=68; RWP N=42)*
2-week, randomized, double-blind, placebo-controlled, crossover **Primary endpoint:** Change from baseline in weekly cataplexy attacks (averaged over 2-week treatment period)	5-week, randomized, double-blind, placebo-controlled **Primary endpoint:** Change from baseline in weekly cataplexy attacks at Week 5	6-month, open-label period[1] followed by 3-week, double-blind, placebo-controlled, randomized withdrawal period **Primary endpoint:** Change from randomization in weekly cataplexy attacks

OLP = open label; RWP = randomized withdrawal period
1. Open-label extension of SYMPHONY

Phase 3 results demonstrate rapid and robust reductions in cataplexy with AXS-12 treatment

SYMPHONY

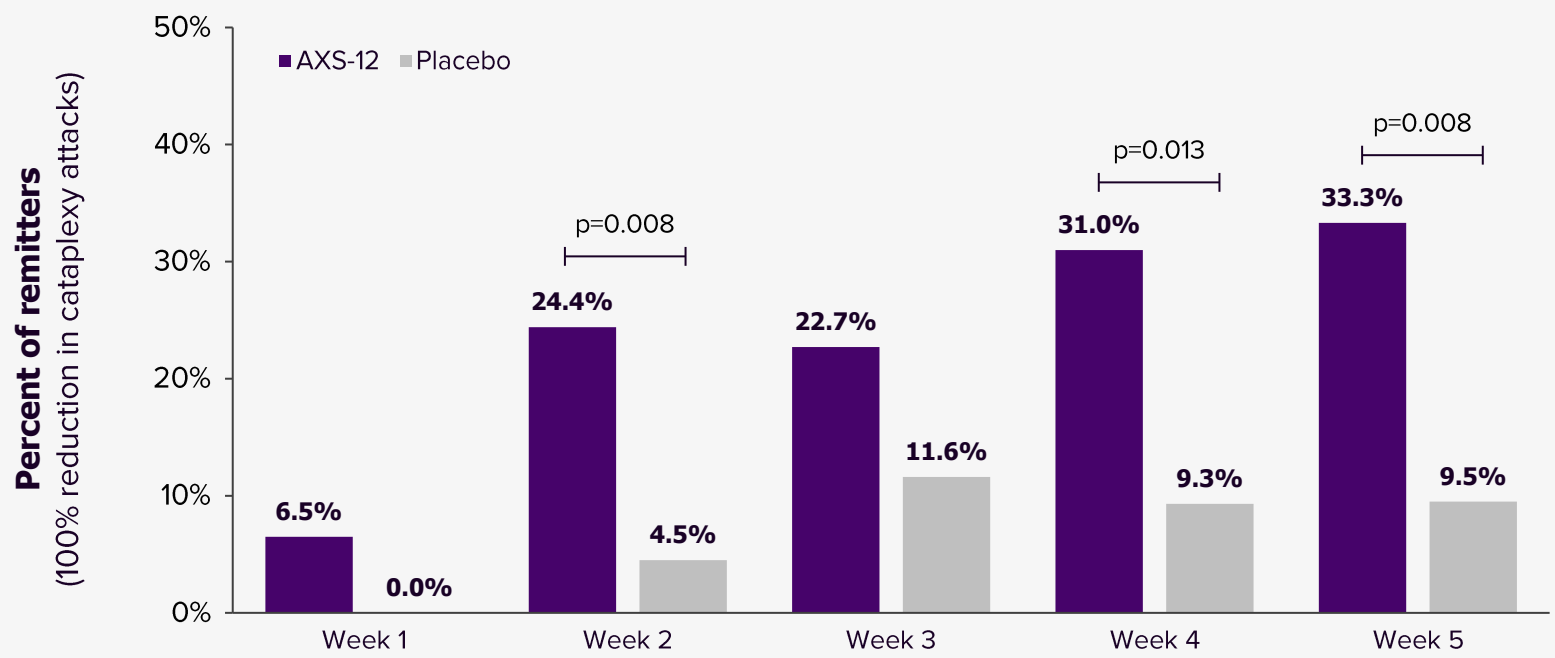
*Ratio of change in the AXS-12 group divided by the ratio of change in the placebo group (rate ratio of 1 = no difference)

Significant reductions in weekly cataplexy attacks compared to placebo starting at Week 1 (p=0.007) and maintained through Week 5 (p=0.018)

Axsome Therapeutics, Inc. Data on file.

Rates of complete cataplexy response were significantly greater with AXS-12 treatment

SYMPHONY

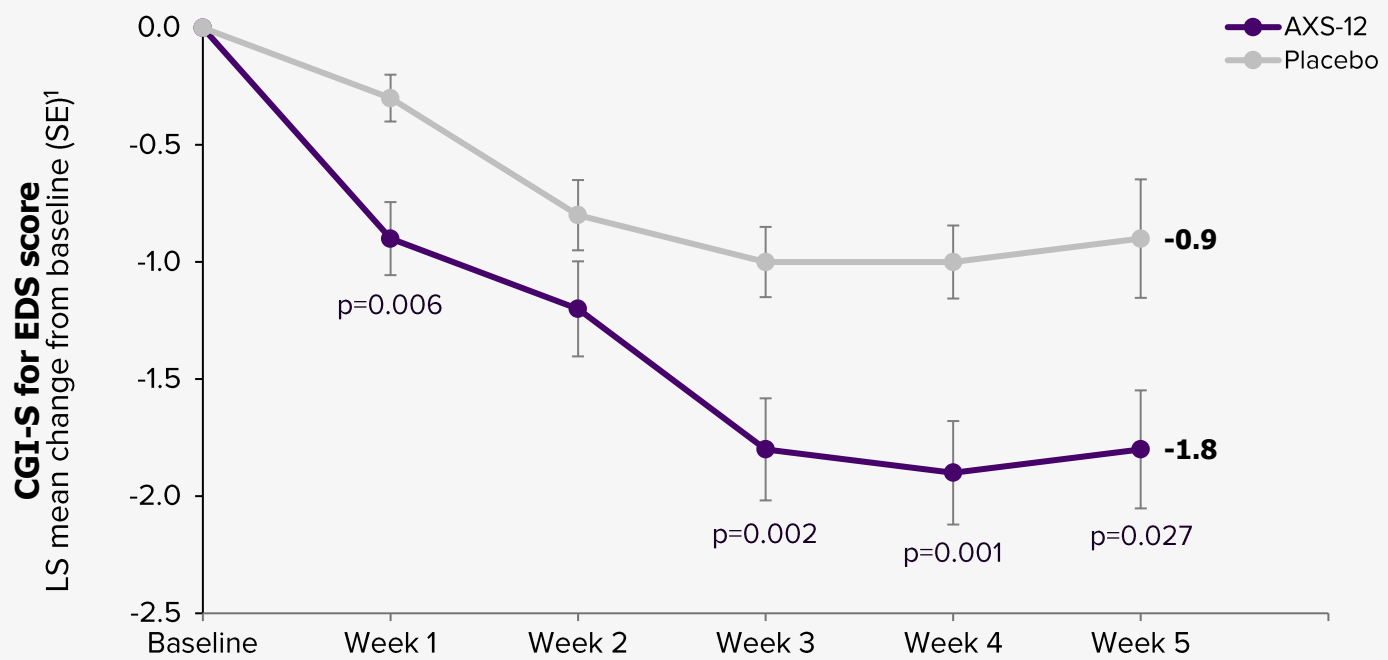


Over 30% of patients treated with AXS-12 achieved remission (100% reduction) in cataplexy attacks by Week 5 compared to <10% of patients treated with placebo (p=0.008)

Axsome Therapeutics, Inc. Data on file.

AXS-12 significantly reduced the severity of excessive daytime sleepiness

SYMPHONY

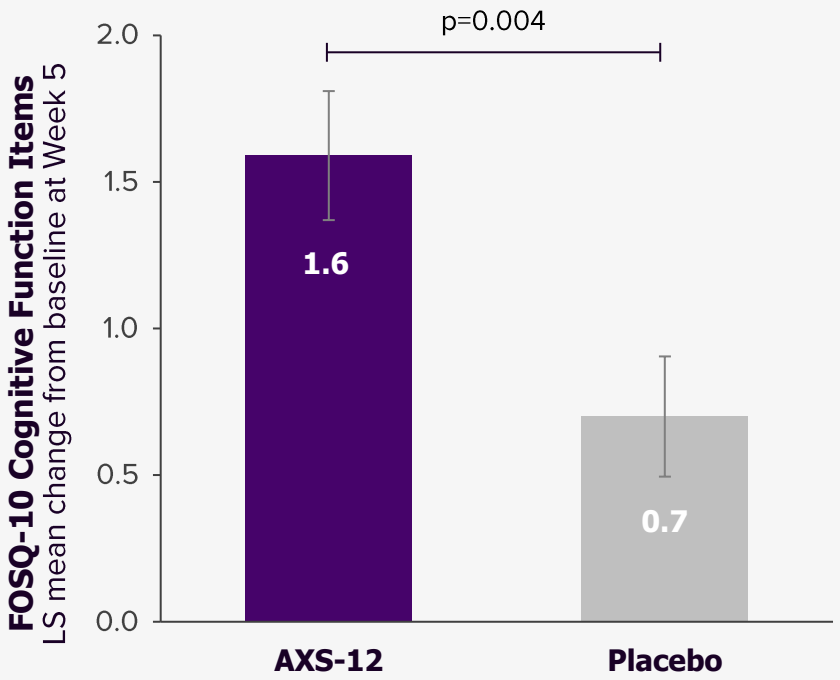


Significant reduction in EDS severity as measured by the CGI-S for EDS score compared to placebo (p=0.027), with improvement observed as early as Week 1 (p=0.006)

1. Wilcoxon rank sum test; Axsome Therapeutics, Inc. Data on file.

AXS-12 led to clinically meaningful improvements in cognitive function

SYMPHONY



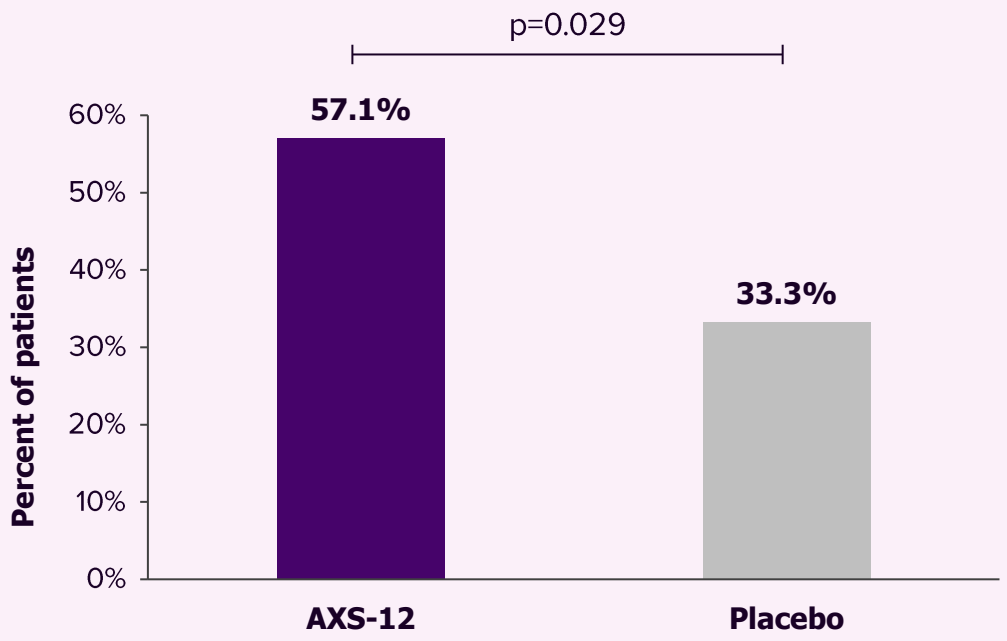
>2x improvement in cognitive function as measured by the FOSQ-10 cognitive function items compared to placebo (p=0.004)

FOSQ-10 = Functional Outcomes of Sleep Questionnaire

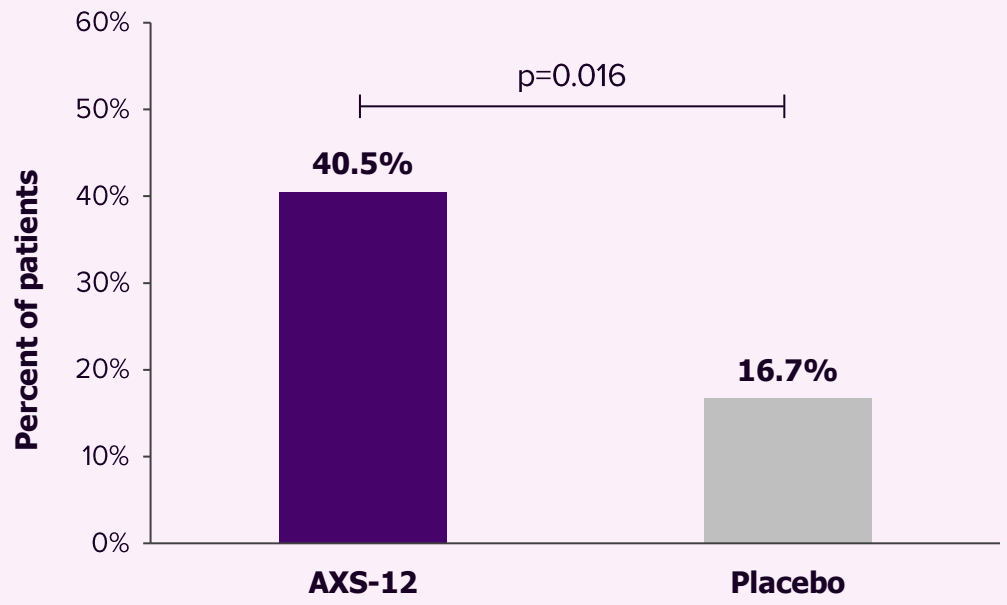
Concurrent relief in core symptoms of narcolepsy with AXS-12

SYMPHONY

Patients achieving clinical response for both cataplexy and EDS at Week 5[1]



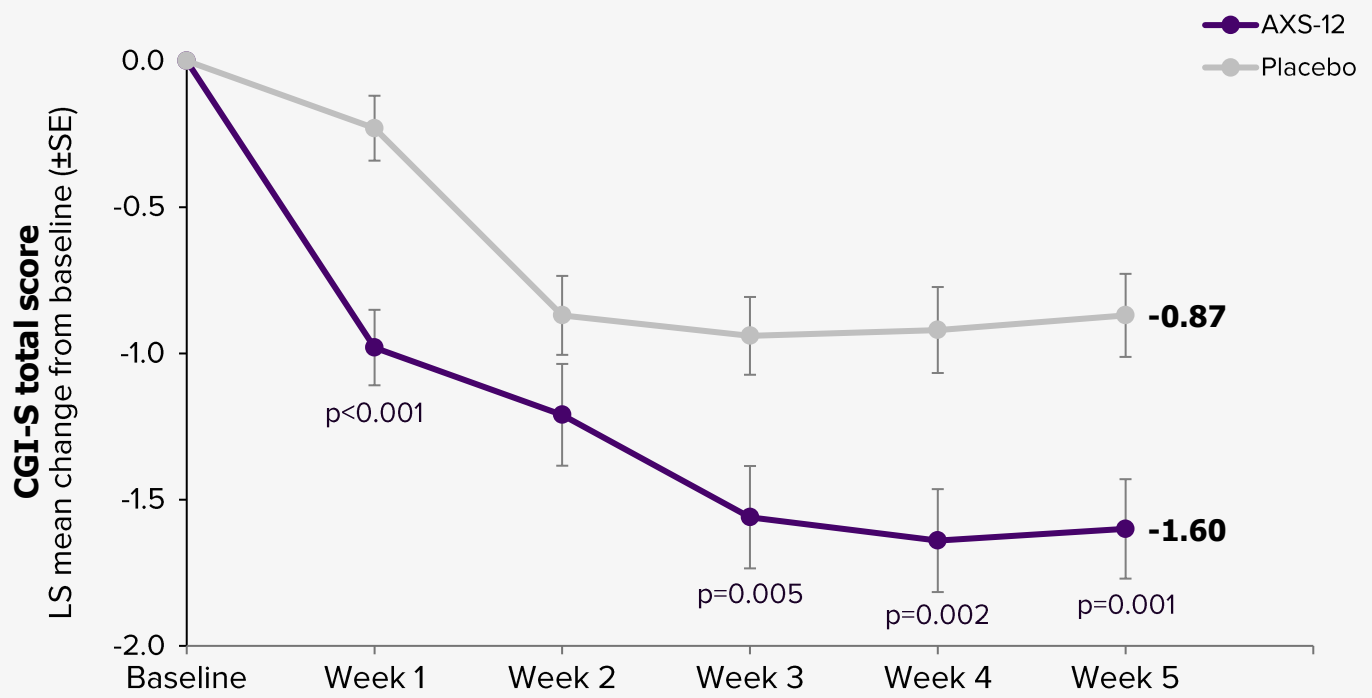
Patients achieving clinical response for both cataplexy and cognitive function at Week 5[2]



1. Defined as ≥50% reduction in weekly frequency of cataplexy attacks and ≥30% reduction in weekly frequency of inadvertent naps; 2. Defined as ≥50% reduction in weekly frequency of cataplexy attacks and any increase from baseline in percent of responding days for Ability to Concentrate score; Axsome Therapeutics, Inc. Data on file.

Improvements in overall narcolepsy severity further support potential for AXS-12 to provide broad symptom relief

SYMPHONY

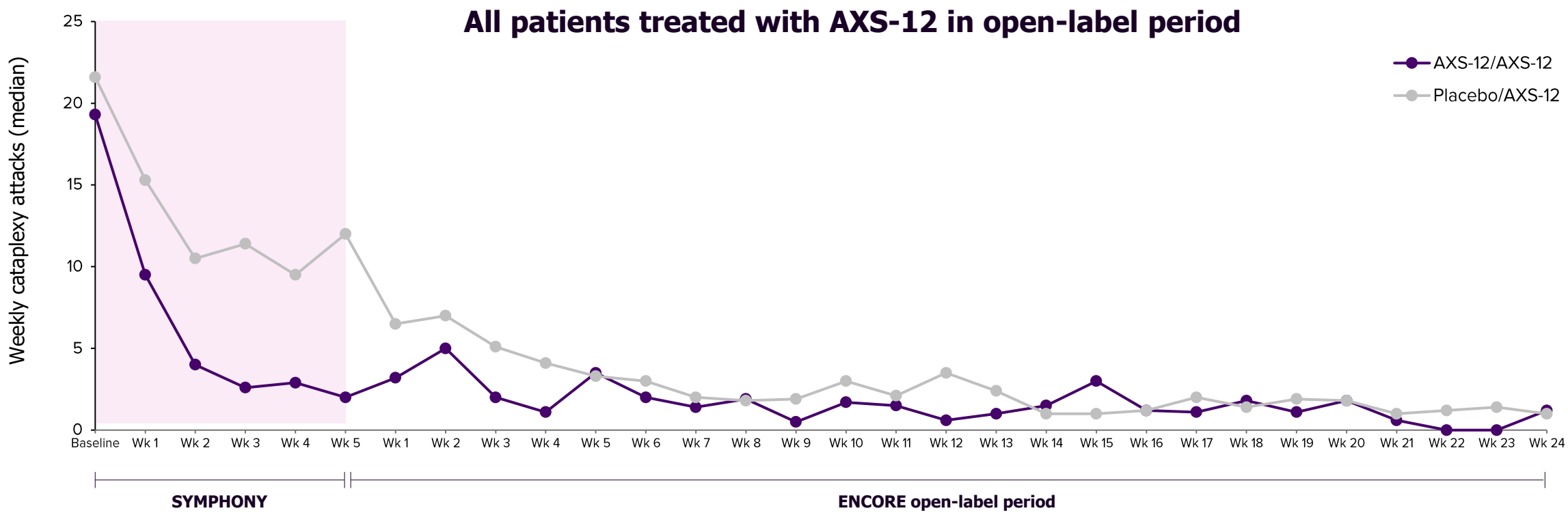


Significant reductions in overall narcolepsy severity as measured by the CGI-S total score compared to placebo at Week 5 (p=0.001), with improvements observed as early as Week 1 (p<0.001)

Axsome Therapeutics, Inc. Data on file.

Reductions in cataplexy attacks were sustained with long-term AXS-12 treatment

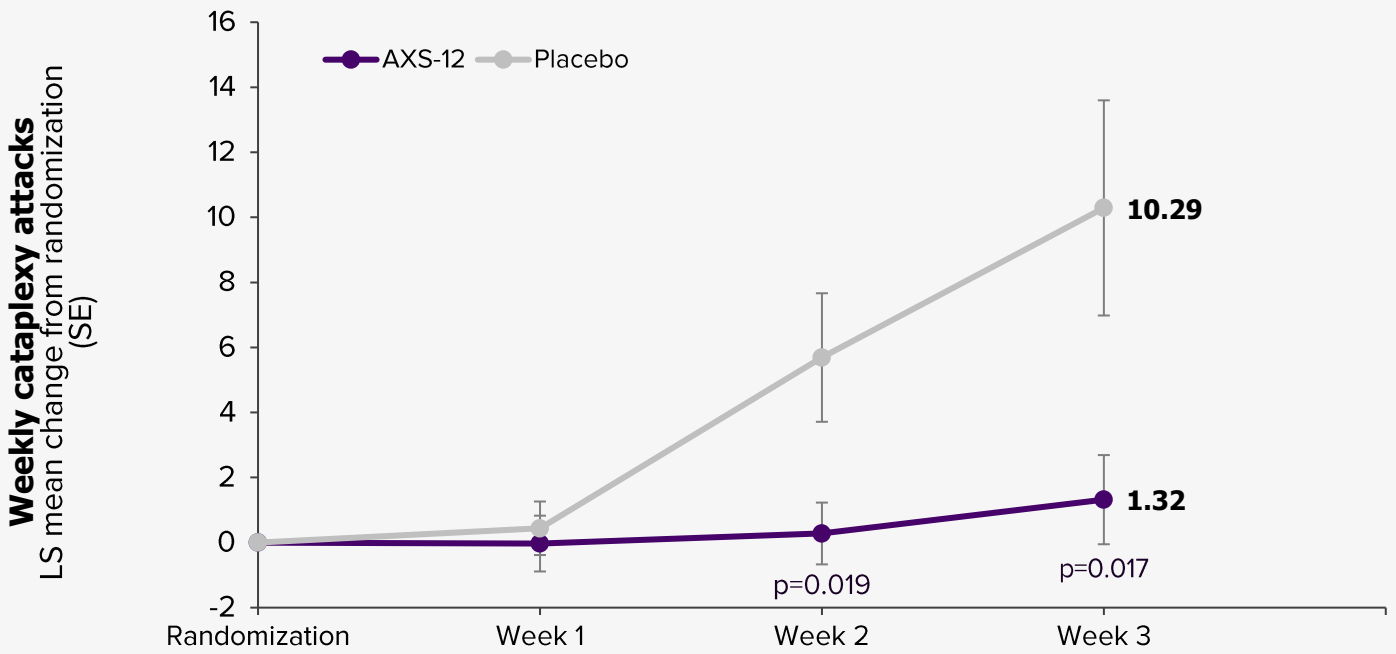
AXS-12/AXS-12 (n)	46	46	45	44	42	42	30	32	29	30	29	28	25	28	22	24	22	24	20	20	17	20	20	23	22	23	20	21	19	20
Placebo/AXS-12 (n)	44	44	44	44	44	43	30	27	26	28	24	24	21	20	20	20	20	21	18	18	21	19	17	18	18	19	14	15	17	13



Axsome Therapeutics, Inc. Data on file.

Significant improvements in cataplexy demonstrated with AXS-12 vs. placebo in randomized withdrawal trial

ENCORE

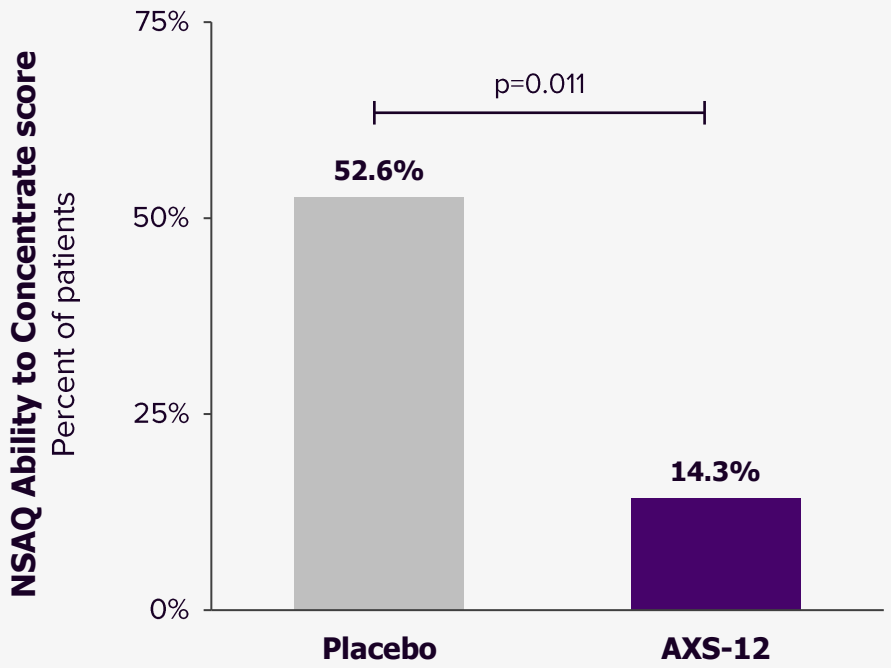


Patients randomized to switch to placebo experienced significant worsening in cataplexy attacks compared to those who continued AXS-12 treatment (p=0.017)

Axsome Therapeutics, Inc. Data on file.

Significant improvements in cognitive function demonstrated with AXS-12 vs. placebo in randomized withdrawal trial

ENCORE

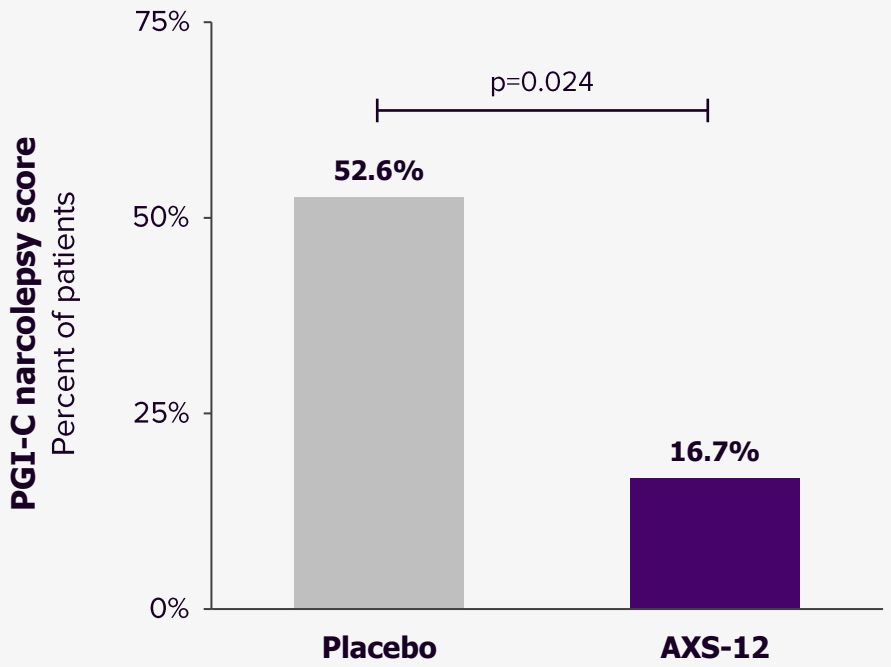


Patients randomized to switch to placebo were significantly more likely to experience worsening in the ability to concentrate compared to those who continued AXS-12 treatment (p=0.011)

Axsome Therapeutics, Inc. Data on file.

Significant improvements in overall narcolepsy demonstrated with AXS-12 vs. placebo in randomized withdrawal trial

ENCORE



Patients randomized to switch to placebo were significantly more likely to report worsening of their narcolepsy symptoms overall compared to those who continued AXS-12 treatment (p=0.024)

Axsome Therapeutics, Inc. Data on file.

AXS-12 was safe and well tolerated across three clinical trials

Low and balanced discontinuation rates due to AEs across three placebo-controlled trials

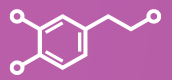
All commonly reported *AEs were mild to moderate* in severity, with no reported serious AEs

Long-term safety and tolerability was *consistent* with the short-term trials and *no new safety signals were observed*

AXS-12 in narcolepsy: Key takeaways

Narcolepsy is a rare and debilitating neurological condition, with up to 70% of patients experiencing cataplexy

Many treated patients continue to experience persistent symptoms including cataplexy, excessive daytime sleepiness, and cognitive impairment



AXS-12 is a novel, selective NRI and cortical dopamine modulator that targets key neurotransmitters involved in sleep-wake regulation, cognition, and maintaining muscle tone during wakefulness

AXS-12 demonstrated consistent, robust efficacy and safety in three placebo-controlled trials

NRI = norepinephrine reuptake inhibitor

AXS-14

Andrea Chadwick, MD, MSc, FASA

Kasumi Arakawa Professor of Anesthesiology, Pain, and Perioperative Medicine | Director of Fibromyalgia and Centralized Pain Exploration (FACE) Lab

| *University of Kansas Medical Center*

axsome

ADVANCING FRONTIERS IN FIBROMYALGIA: Redefining the standard of care

Fibromyalgia (FM)

An estimated *~17 million* people in the U.S. are impacted by fibromyalgia[1]

Chronic and debilitating neurological pain syndrome resulting from a dysfunction in central pain processing[2,3]

Characterized by widespread musculoskeletal pain, fatigue, disturbed sleep, mood disturbances, cognitive impairment, and hypersensitivity to sensory sitmuli[4,5]

Associated with substantial physical disability and reduced emotional and social wellbeing, financial burden, and reduced quality of life[2,3]

1. Vincent, et al. *Arthritis Care Res (Hoboken)* 2013; 3. Choy E, et al. *BMC Health Serv Res.* 2010; 3. Arnold LM, et al. *Patient Educ Couns.* 2008; 4. Bair MJ & Krebs EE. *Ann Intern Med.* 2020; 5. Clauw DJ. *Ann Rheum Dis.* 2024

Recent advances in nomenclature: nociplastic pain[1,2]

> Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain

Introduced in 2016 through the International Association for the Study of Pain Terminology Task Force

Formal definition of third pain mechanism distinct from nociceptive and neuropathic pain arising from central sensitization

Best exemplified in conditions including:

- Fibromyalgia
- Irritable bowel syndrome
- Migraine and tension headache
- Chronic low back pain, and others

1. Kaplan CM, et al. *Nature Reviews Neurology* 2024; 2. Arnold, et al. Clin J Pain 2016; 3. Kosek, et al. *Pain* 2024; 4. Harte SE, et al. *J Appl Behav Res.* 2018

Barriers to diagnosis often limits access to timely and adequate care of fibromyalgia[1-5]

- Heterogeneous condition with broad array and severity of symptoms
- High overlap with other comorbidities
- Stigmatization and limited social recognition of the disorder
- Inconsistencies in treatment practices for fibromyalgia

~6 Years from initial presentation of symptoms to receiving an actual diagnosis of fibromyalgia[2]

~4 Average number of physicians patients present to prior to receiving a diagnosis[1]

>1/3 Of patients may present to more than *three* physicians prior to receiving a diagnosis[1]

1. Choy E, et al. *BMC Health Serv Res.* 2010; 2. Weinstein J, et al. *J Rheumatol.* 2024; 3. Liu Y, et al. *J Manag Care Spec Pharm.* 2016; 4. Arnold LM, et al. *Int J Clin Pract.* 2016; 5. Colombo B, et al. *J Adv Nurs.* 2025

Fibromyalgia has a profound impact across all aspects of patients' lives

Fibromyalgia is associated with:

Lost days at work due to fibromyalgia symptoms[1]

Reduced quality of life, social, and occupational functioning[1,2]

Greater overall health status impairment vs. other chronic pain conditions[1]

High rates of comorbid medical and psychiatric symptoms[3,4]

More frequent emergency room visits, outpatient visits, and hospitalizations[3]

Higher rates of polypharmacy[1,4,5]

Increased healthcare utilization[1]

1. Choy E, et al. *BMC Health Serv Res.* 2010; 2. Arnold LM, et al. *Patient Educ Couns.* 2008; Arnold LM, et al. *Int J Clin Pract.* 2016; Robinson RL, et al. *Pain Med.* 2013; Giorgi V, et al. *Curr Pain Headache Rep.* 2024

FDA The Voice of the Patient

Top two symptoms FM patients report as having the greatest impact on their or their loved one's life[1]:

Widespread pain

- "Climbing a couple of stairs is agonizing. My leg muscles feel leaded, stiff, and weak, and almost as if they are going to rip if I continue to walk."
- "The pain is so bad… It feels like there are knives sticking into my body."

Fatigue

- "I literally hit a brick wall…all of a sudden I come to a complete and total stop."
- "The fatigue is just so completely and totally overwhelming that it is hard to even have the energy to breathe."

Impact on daily life

- Worry about the future, suicidal thoughts, and social isolation
- Ability to perform at work
- Reliance on caregivers for daily activities
- Significant, often debilitating, impact on relationships

Key challenges and unmet needs in the management of fibromyalgia

Fibromyalgia management requires a multidisciplinary and patient-centric approach including both pharmacological and non-pharmacological interventions[1,2]

Commonly prescribed pharmacological interventions include a wide variety of medications[2,3]:

- SNRIs/SSRIs, muscle relaxants, opioids, anticonvulsants, TCAs
- FDA-approved medications account for <1/3 of ACR-recommended pharmacotherapies used to manage FM symptoms

Limitations of current treatments:

- High rates of patient dissatisfaction due to inadequate symptom control and/or tolerability issues lead to poor adherence, switching, and polypharmacy[1-5]
  - >3/4 of treated FM patients rely on multiple concurrent medications to manage different symptoms[6]
  - >50% of FM patients discontinue treatment within the first year[3]

Only 3 FDA-approved products for fibromyalgia, with no therapeutic innovation in the last 15 years

TCA = tricyclic antidepressants

1. Arnold LM, et al. *Int J Clin Pract.* 2016; 2. Giorgi V, et al. *Curr Pain Headache Rep.* 2024; 3. Liu Y, et al. *J Manag Care Spec Pharm.* 2016; 4. Lauche R, et al. *Clin Exp Rheumatol.* 2013; 5. Choy E, et al. *BMC Health Serv Res.* 2010; 6. Robinson RL, et al. *Pain Med.* 2012

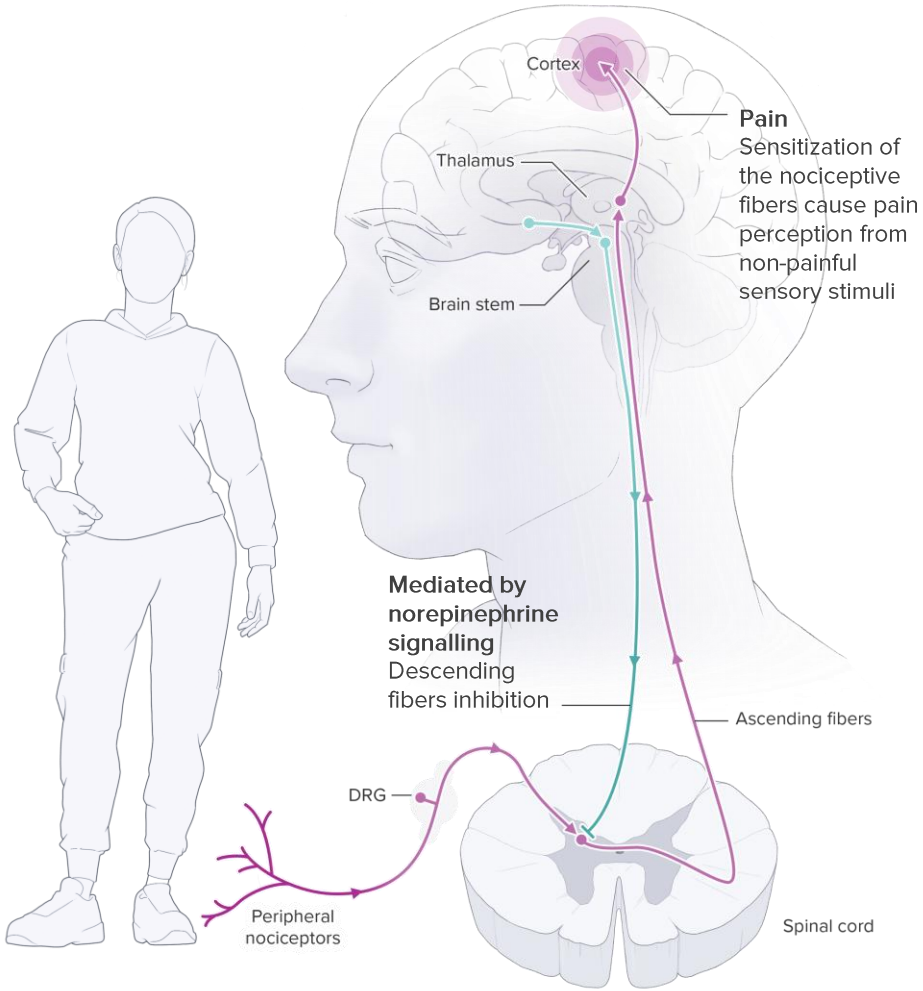
AXS-14 (esreboxetine)

Novel pharmacological approach for the management of fibromyalgia (FM)

Fibromyalgia pain is thought to be partially caused by *dysregulated signaling* in the descending analgesic system[1,2]

Norepinephrine, one of the key neurotransmitters in this pathway, has predominantly *pain-inhibitory effects*[1,2]

AXS-14 is a *more potent* and *selective* enantiomer of racemic reboxetine that inhibits the reuptake of norepinephrine, resulting in increased norepinephrine activity and decreased pain signaling



Adapted from Siracusa R, et al. Int. J. Mol. Sci. 2021

1. Clauw D, *Mayo Clin Proc* 2015; 2. Siracusa R, et al. *Int J Mol Sci.* 2021

Phase 2 and Phase 3 trials of AXS-14 in fibromyalgia

Phase 2 (N=267)	Phase 3 (N=1122)
Efficacy and safety of AXS-14 vs. placebo in patients with fibromyalgia	

Randomized, double-blind, placebo-controlled trial

- 8-week, flexible dose
- **Primary endpoints:**
  - Weekly mean pain scores
  - FIQ total score
  - PGI-C score

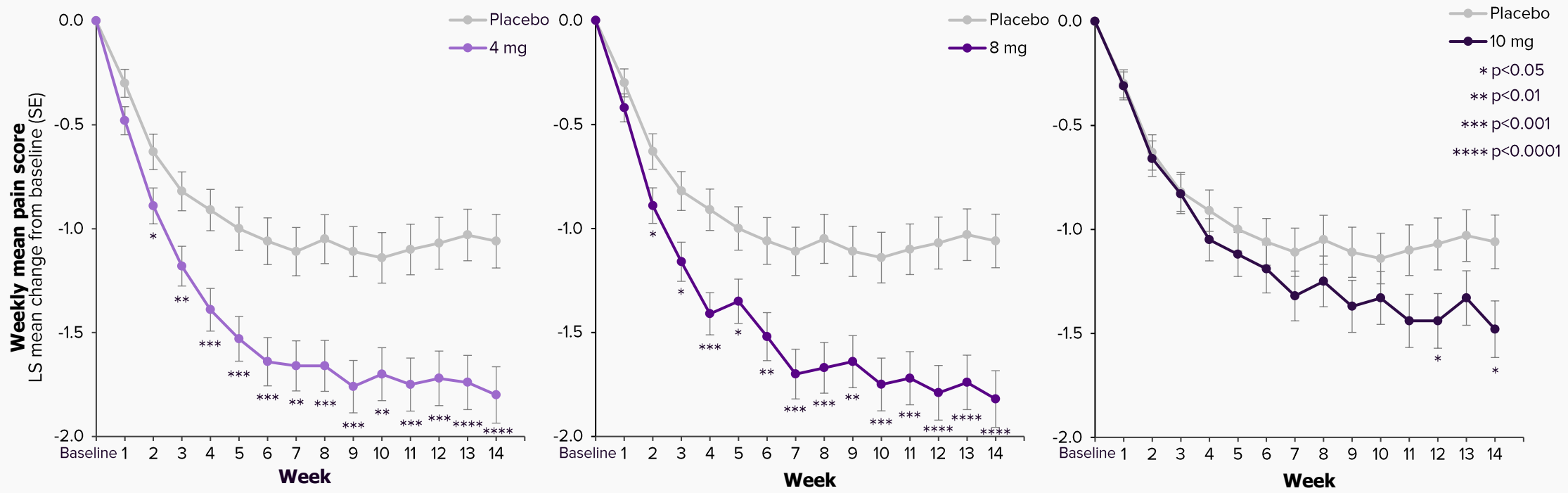
Randomized, double-blind, placebo-controlled trial

- 12-week[1], fixed dose
- **Primary endpoints:**
  - Weekly mean pain scores
  - FIQ total score
- **Key secondary endpoints:**
  - PGI-C score
  - Modified GFI score
  - SF-36 physical functioning domain

FIQ = Fibromyalgia Impact Questionnaire; PGI-C = Patient Global Impression of Change; GFI = Global Fatigue Index; SF-36 = 36-item Short-Form health survey
1. Trial included 2-week dose titration period followed by a 12-week fixed-dose period

Rapid and robust efficacy demonstrated in Phase 3 trial of AXS-14 in fibromyalgia

Pain reduction

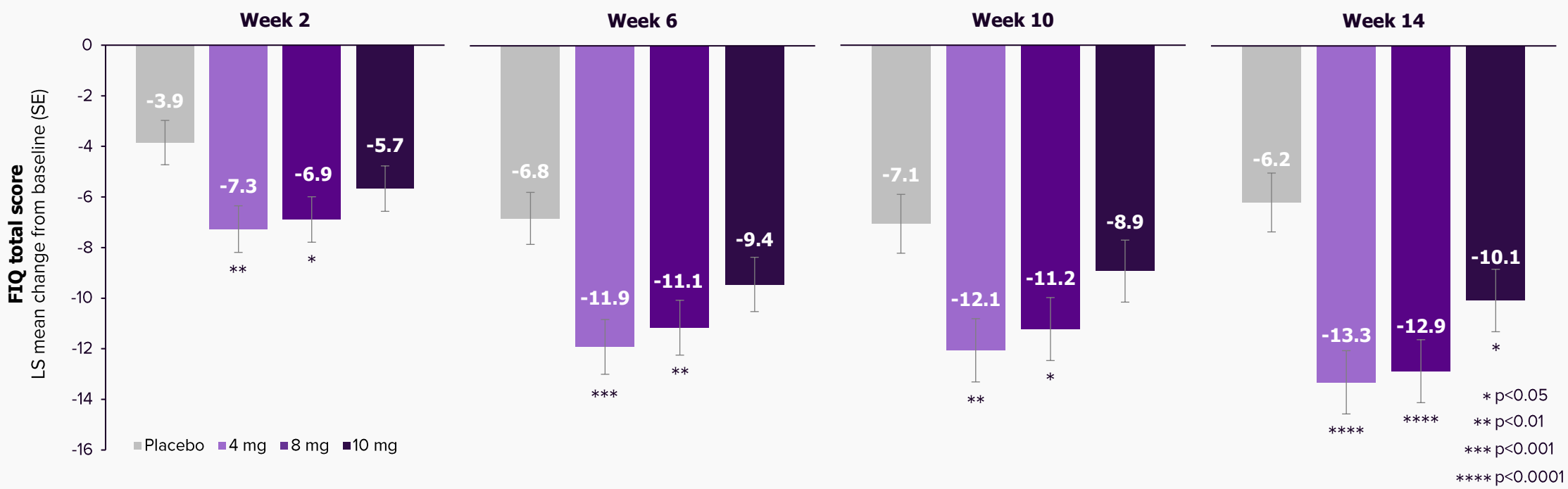


Significant reductions in weekly mean pain scores compared to placebo at Week 14 (p<0.0001 to p=0.02)

Axsome Therapeutics, Inc. Data on file.

Improvements in patient functioning and well-being with AXS-14 treatment in Phase 3 trial

Improved patient functioning over time

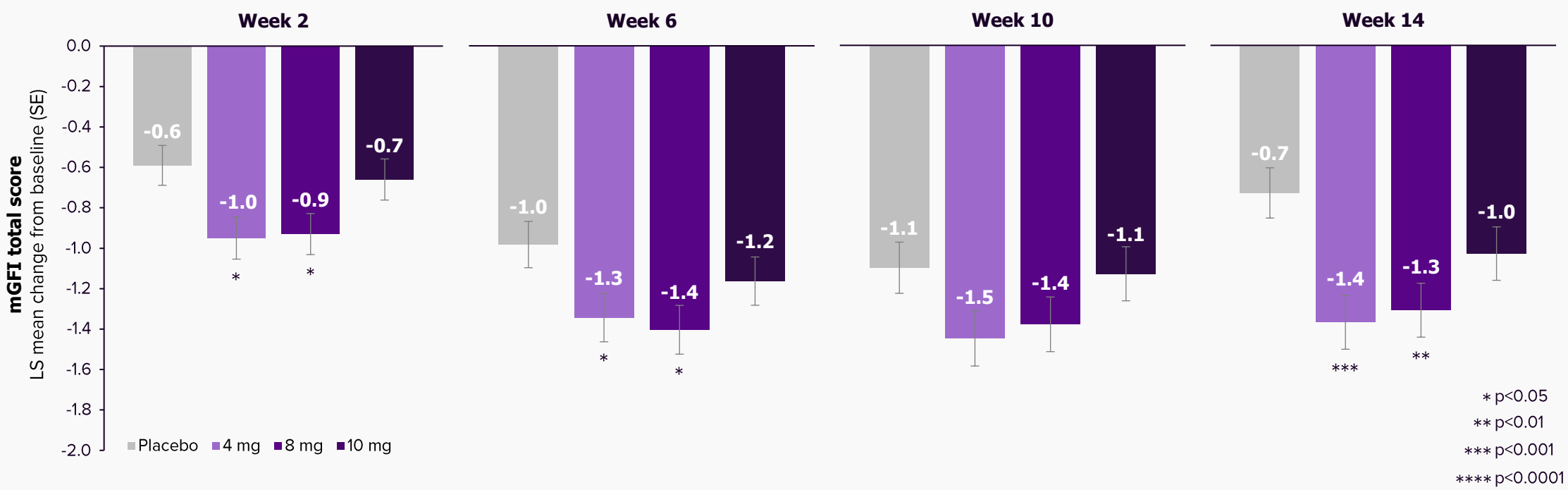


Significant reductions in patient functioning and well-being as measured by the FIQ total score compared to placebo at Week 14 ($p<0.0001$ to $p=0.02$)

FIQ = Fibromyalgia Impact Questionnaire
Axsome Therapeutics, Inc. Data on file.

Improvements in fatigue with AXS-14 treatment in Phase 3 trial

Reduced fatigue over time

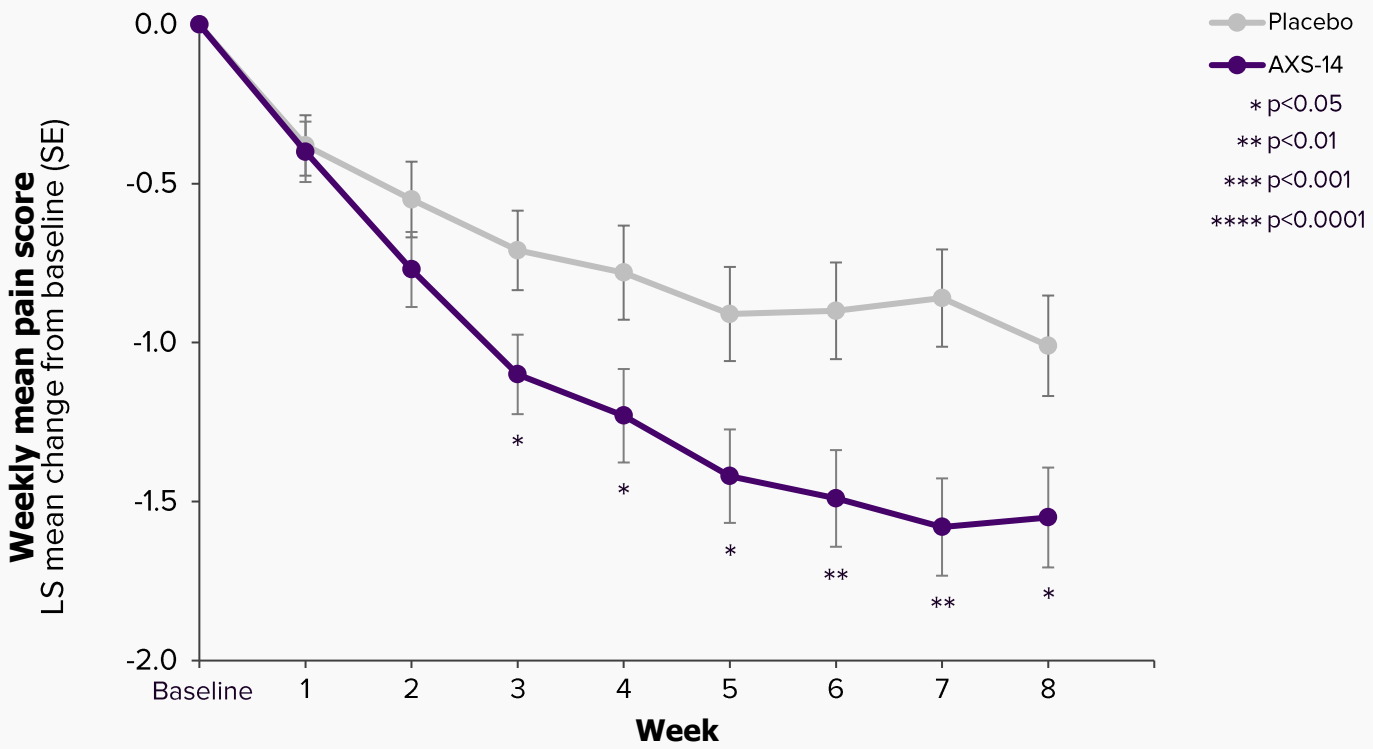


Reductions in fatigue as measured by the GFI total score compared to placebo at Week 14 (4 mg, p=0.0005; 8 mg, p=0.001)

mGFI = Modified Global Fatigue Index
Axsome Therapeutics, Inc. Data on file.

Phase 2 results demonstrate rapid reductions in fibromyalgia pain with AXS-14 treatment

Pain reduction

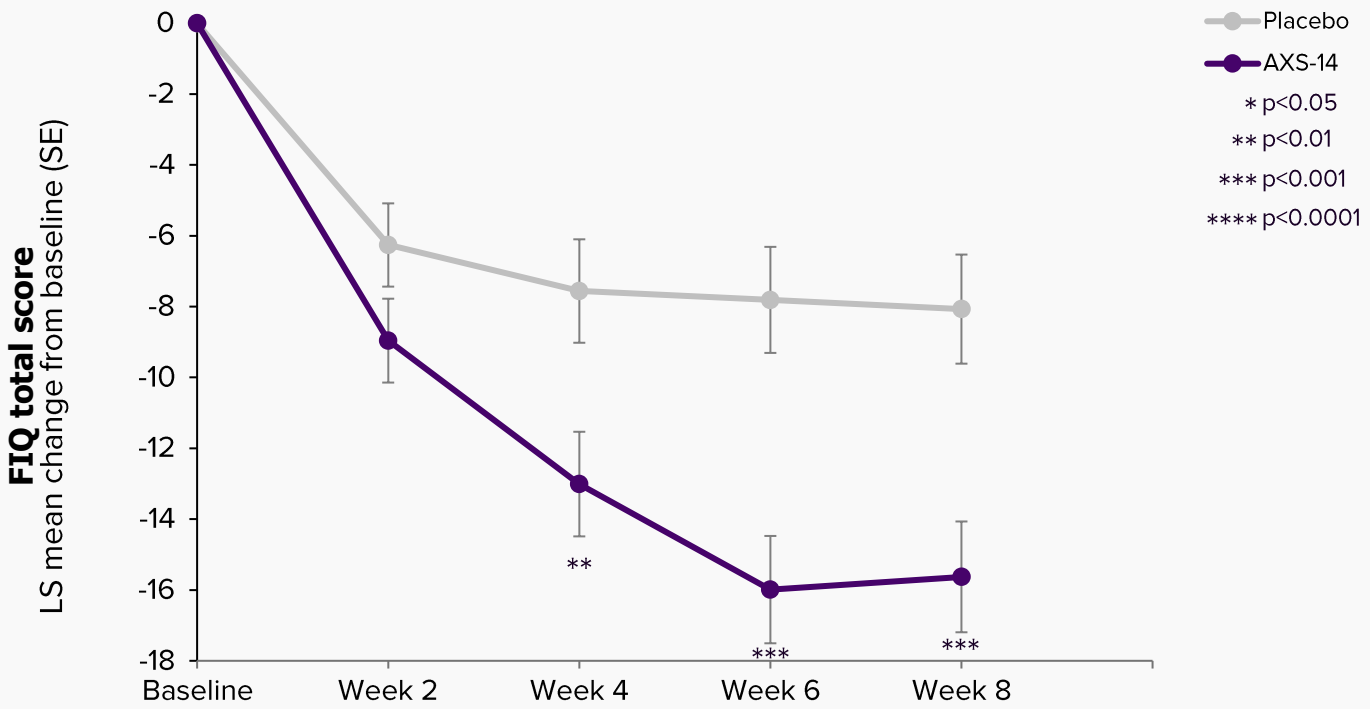


Statistically significant reductions in weekly mean pain scores compared to placebo starting at Week 3 and maintained through Week 8 (p=0.01)

Axsome Therapeutics, Inc. Data on file.

Phase 2 results demonstrate improvements in patient functioning and overall well-being

Improved patient functioning

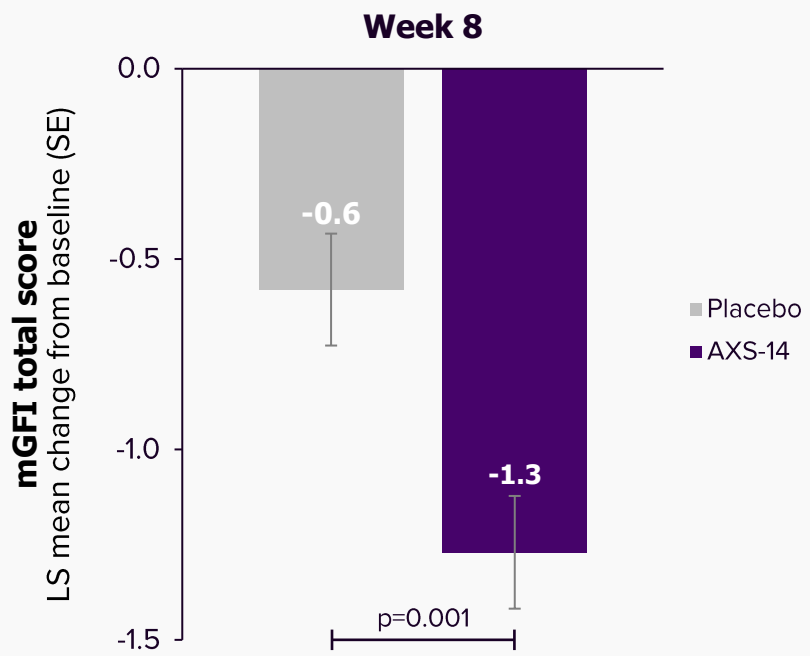


Significant improvements in patient functioning and well-being as measured by the FIQ total score compared to placebo at Week 8 (p=0.0007)

FIQ = Fibromyalgia Impact Questionnaire
Axsome Therapeutics, Inc. Data on file.

Phase 2 results demonstrate significant reductions in fatigue

Reduced fatigue



Substantial reduction in fatigue as measured by the GFI index compared to placebo at Week 8 (p=0.001)

mGFI = Modified Global Fatigue Index
Axsome Therapeutics, Inc. Data on file.

AXS-14: Key takeaways

Fibromyalgia is a chronic and debilitating neurological pain syndrome that affects an estimated ~17 million people in the U.S.

Fibromyalgia presents with a broad range of symptoms that significantly impact overall patient function, often leading to disability, reduced QoL, and high healthcare utilization

Existing treatments are associated with inadequate symptom control and/or tolerability issues for many patients, leading to high rates of treatment discontinuation and polypharmacy

AXS-14 represents a novel pharmacological approach for the management of fibromyalgia that may address critical gaps in care and meaningfully improve patient outcomes

SYMBRAVO®

Stewart J. Tepper, MD

Vice President of the New England Institute for Neurology and Headache | Professor of Neurology

| *Geisel School of Medicine at Dartmouth*

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ADVANCING FRONTIERS IN MIGRAINE: Novel multi-mechanistic approach targeting unmet needs

Addressing the unmet medical needs of patients living with migraine

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

>80% of patients discontinue their acute migraine treatment in the first 12 months[4]

3 in 4 patients report inadequate response to their oral acute migraine medication[5]

Leading cause of disability among neurological disorders in the U.S., affecting approximately ***39M people***[1,2]

Characterized by recurrent attacks of ***pulsating, often severe and disabling head pain*** associated with nausea, sensitivity to light, and sensitivity to sound[3]

High patient dissatisfaction due to ***limited efficacy*** and/or ***burdensome side effects***

1. American Migraine Foundation 2023; 2. Steiner TJ, et al. *J Headache Pain* 2020; 3. Headache Classification Committee of the International Headache Society (IHS) *Cephalagia* 2018; 4. Symphony Health Claims, New to Brand Patients 2022-2023; 5. Lipton RB, et al. *Headache* 2019

Migraine pathophysiology involves multiple interrelated mechanisms

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(meloxicam and rizatriptan)
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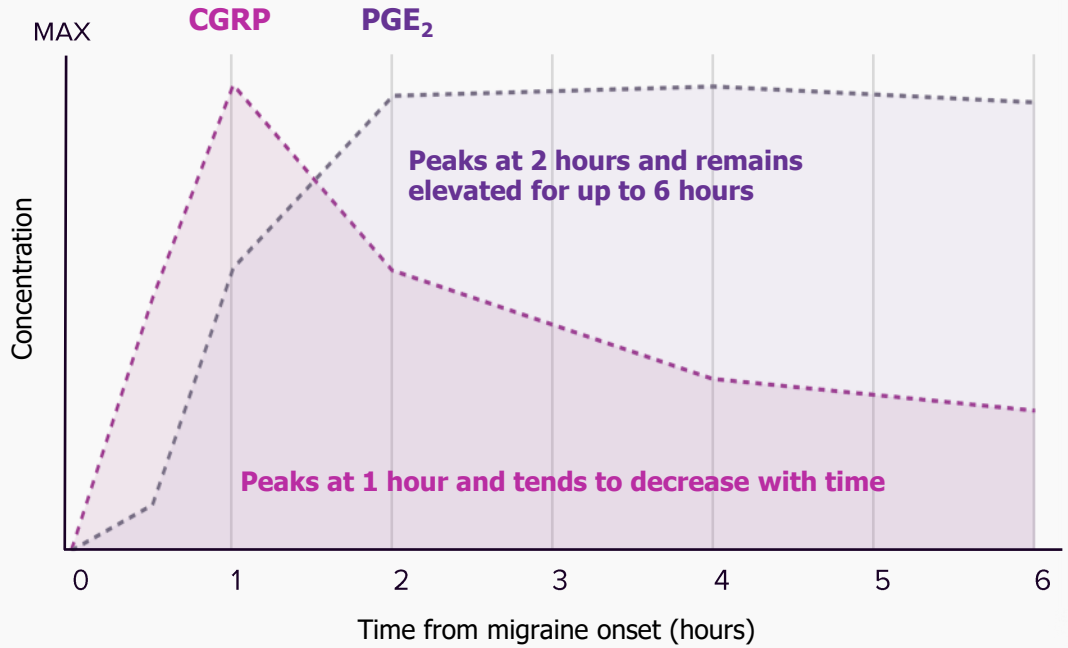
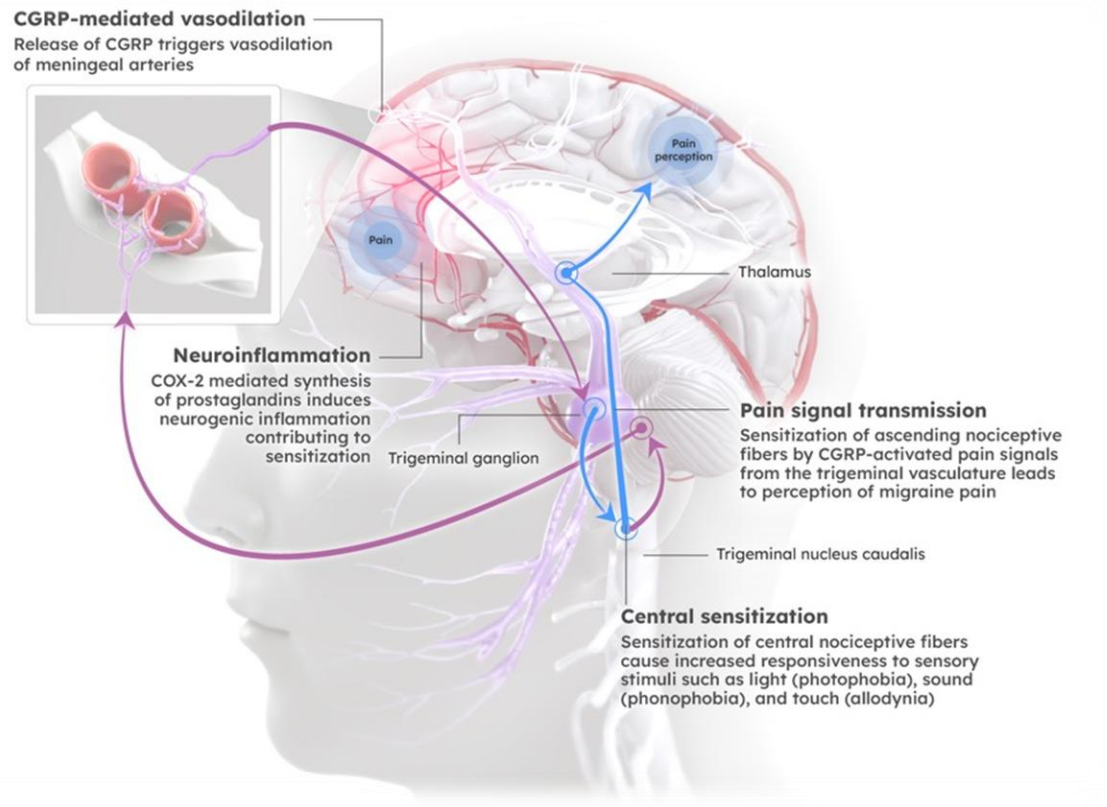
Time Course of CGRP, PGE_2 in Migraine





Most acute treatments don't adequately address the complexity of migraine pathophysiology

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

Recent migraine drug development has *largely focused* on CGRP-related mechanisms

Ergots	Broad serotonin, adrenergic, and dopamine receptor agonism	
Triptans	Serotonin 5-HT1B/1D agonism	prevent CGRP release
Ditans	Serotonin 5-HT1F agonism	prevent CGRP release
Gepants	CGRP receptor antagonism	inhibit CGRP binding

Triptans and gepants *don't directly affect* prostaglandin-mediated inflammatory processes

Prostaglandins are another key mediator of migraine that *drives neuroinflammation* contributing to peripheral and central sensitization, which may occur within 2 hours after attack onset

NSAIDs like meloxicam *inhibit the production* of prostaglandins but don't work effectively for acute treatment of migraine due to their slow onset

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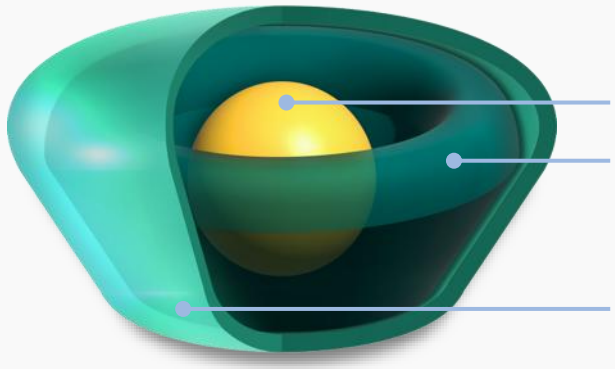
Rapidly absorbed, multi-mechanistic medicine for the acute treatment of migraine

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

MoSEIC™ TECHNOLOGY



Meloxicam

Cyclodextrin carrier molecule
- Hydrophilic outer surface
- Lipophilic cavity

pH modifying buffer

Meloxicam preferentially inhibits COX-2 leading to *reduced neuroinflammation*, interrupting the inflammatory and nociceptive cascades that contribute to *central sensitization*

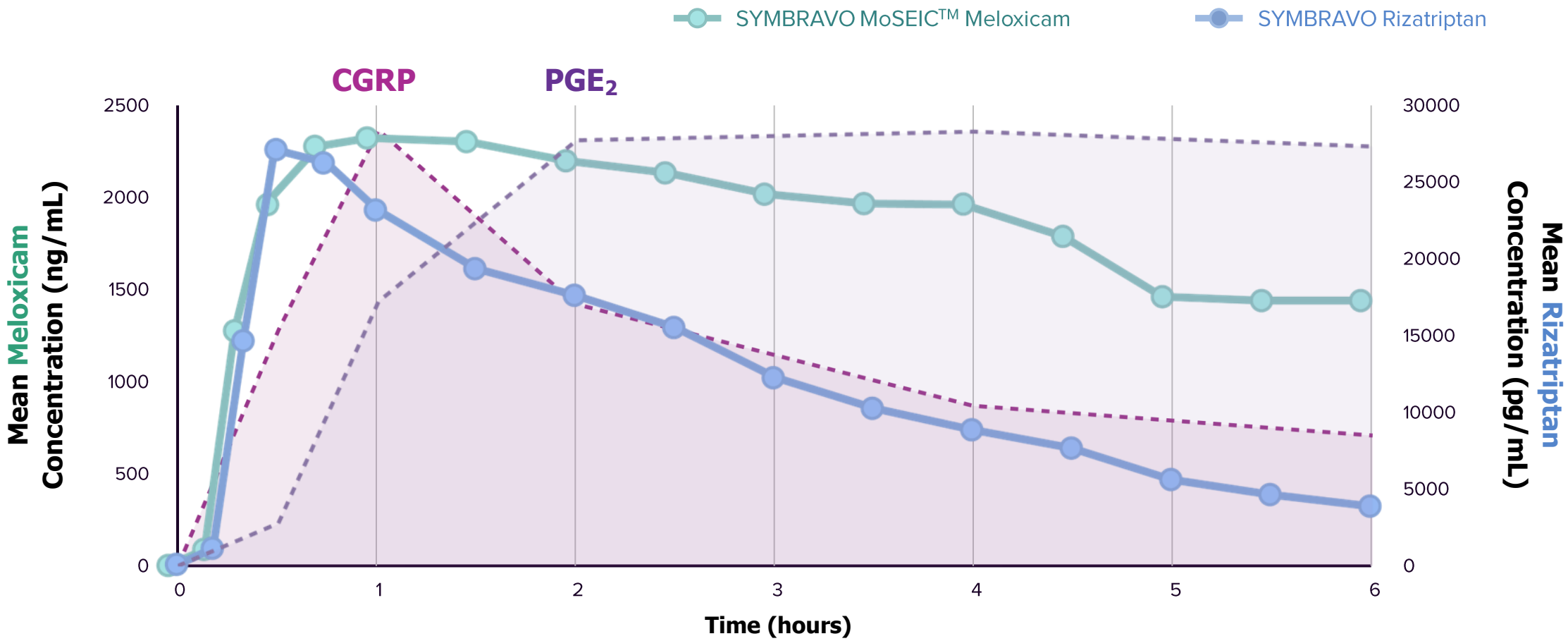
Rizatriptan is a 5-$HT_{1B/1D}$ receptor agonist that inhibits the release of CGRP resulting in *reduced pain signal transmission* to the brain and *reversed vasodilation* of meningeal blood vessels

SYMBRAVO harnesses Axsome's MoSEIC™ technology that *improves the absorption* of meloxicam while maintaining its extended half life

Sources: Geppetti, P. et al. J Headache Pain (2012); COX-2 data from Li, M.M. et al. Med Sci Monit. (2017); PGE2 data from Sarchielli, P. et al. Cephalalgia (2000); Data from Burstein, R., Cutrer, M.F., & Yarnitsky, D. Brain (2000)

Timing of peak plasma levels align with key mediators of migraine pain

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets



CGRP = calcitonin gene-related peptide; MoSEIC = Molecular Solubility Enhanced Inclusion Complex; PGE2 = prostaglandin E2;

1. O'Gorman C, et al. Symbravo (MoSEIC™ meloxicam/rizatriptan): novel oral therapeutic in clinical development for the acute treatment of migraine. Poster presented at: 19th Congress of the International Headache Society; September 5-8, 2019; Dublin, Ireland. 2. Sarchielli P, et al. Cephalalgia. 2000;20(10):907-918.

Robust improvements in migraine symptoms across a broad range of patient profiles

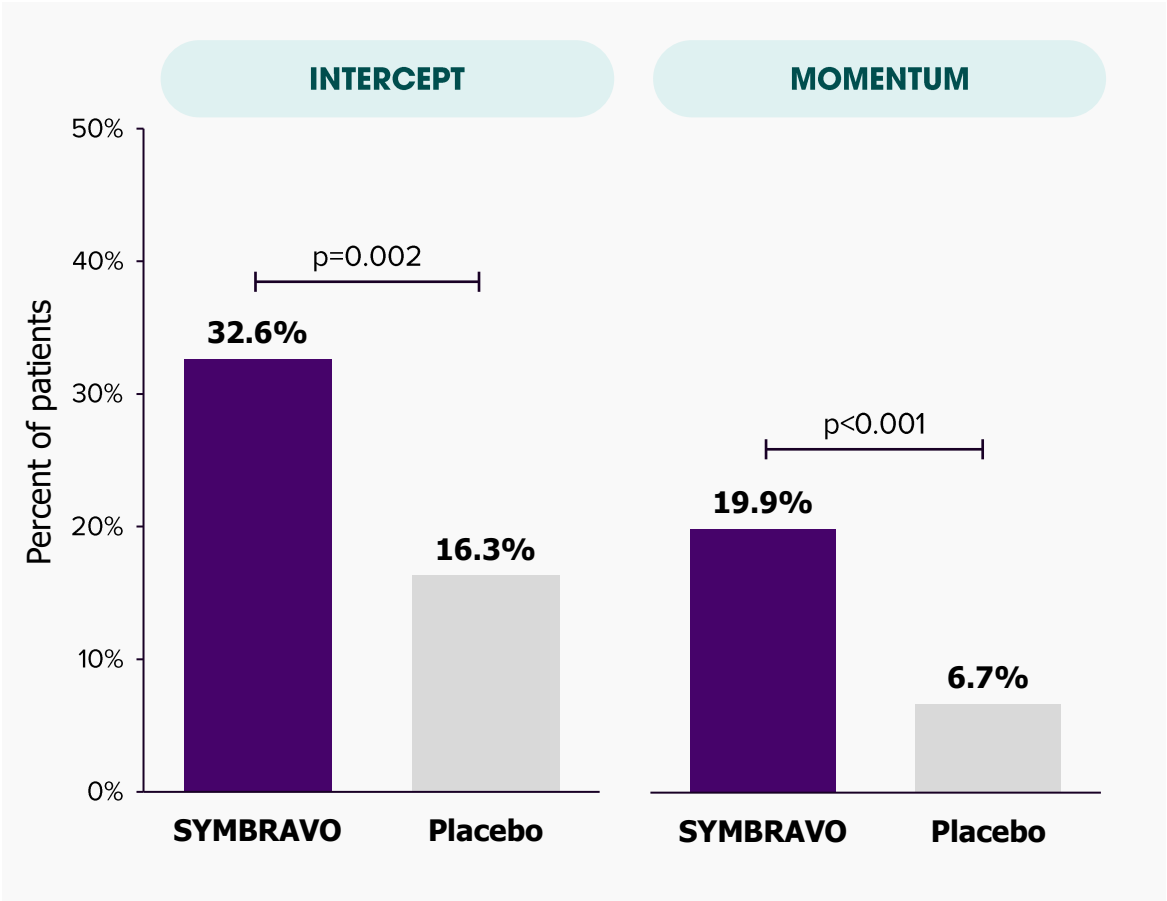
SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

INTERCEPT N=302	MOMENTUM N=1594	EMERGE N=96
Phase 3, randomized, double-blind, placebo-controlled	Phase 3, randomized, double-blind, active- & placebo-controlled	Phase 3, open-label
Earliest onset of migraine pain, while pain is *mild*	*Moderate or severe* migraine pain, with a history of inadequate response to an acute treatment	History of *inadequate response* to an oral CGRP inhibitor
Substantially greater percent of patients achieved pain freedom and MBS freedom at 2 hours with SYMBRAVO vs. placebo		Substantially more patients achieved greater symptom control with SYMBRAVO vs. their prior oral CGRP inhibitor
A single dose of SYMBRAVO provided sustained efficacy through 24 and 48 hours and the ability to quickly return to normal activities		

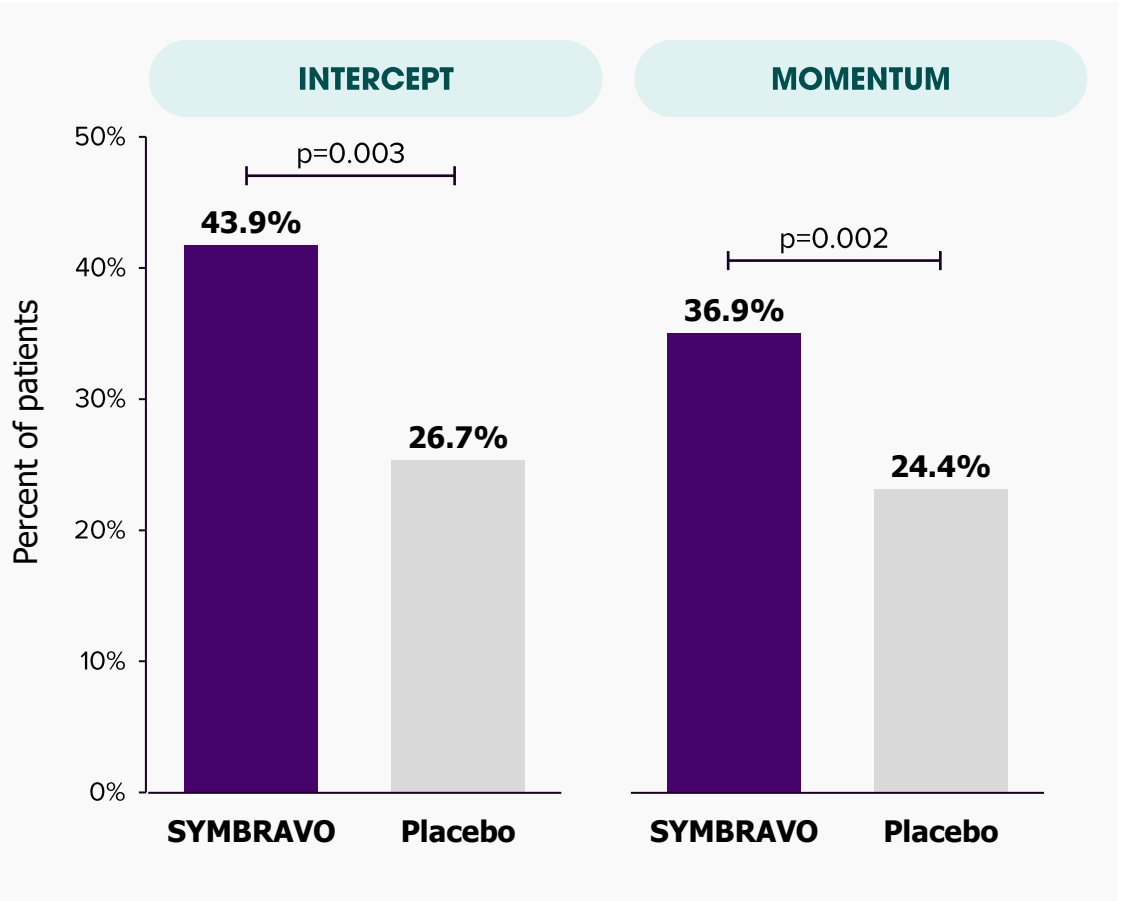
Rapid, robust efficacy results in two Phase 3 trials

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

Pain freedom at 2 hours



MBS freedom at 2 hours

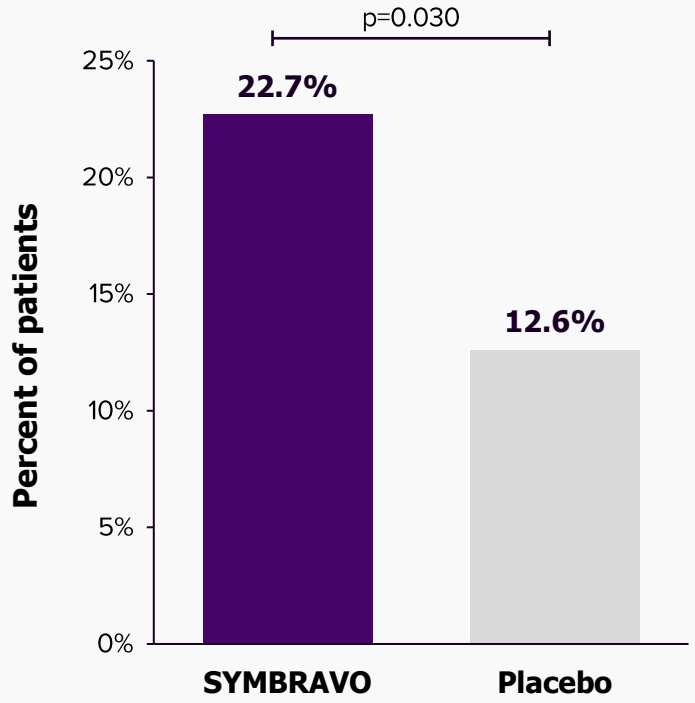


Axsome Therapeutics, Inc. Data on file.

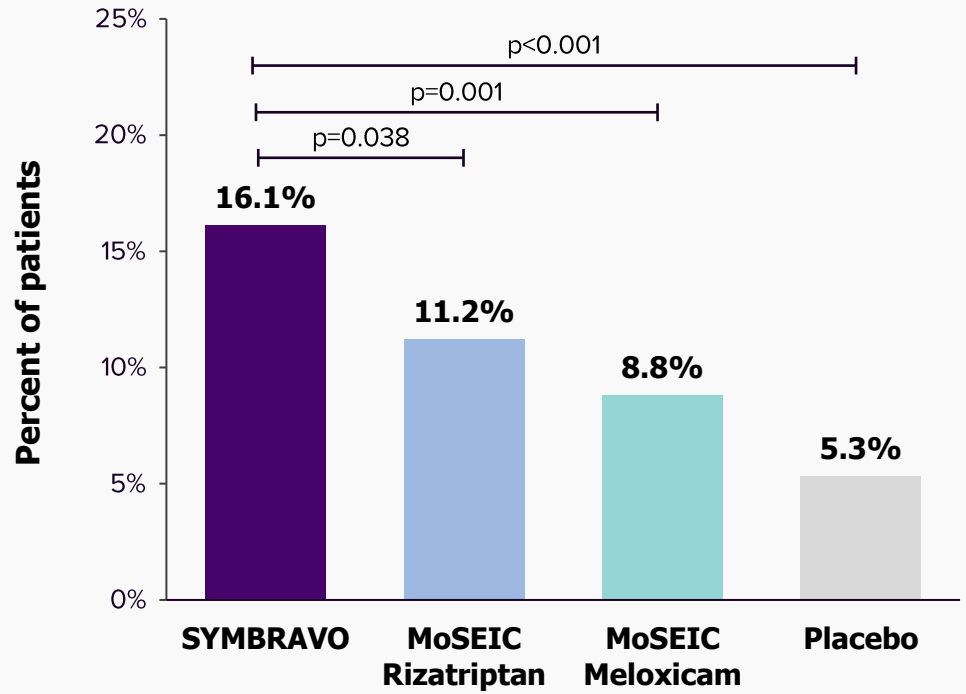
Sustained pain freedom

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

INTERCEPT



MOMENTUM



70% and 81% of patients who achieved pain freedom at 2 hours remained pain free through 24 hours with SYMBRAVO

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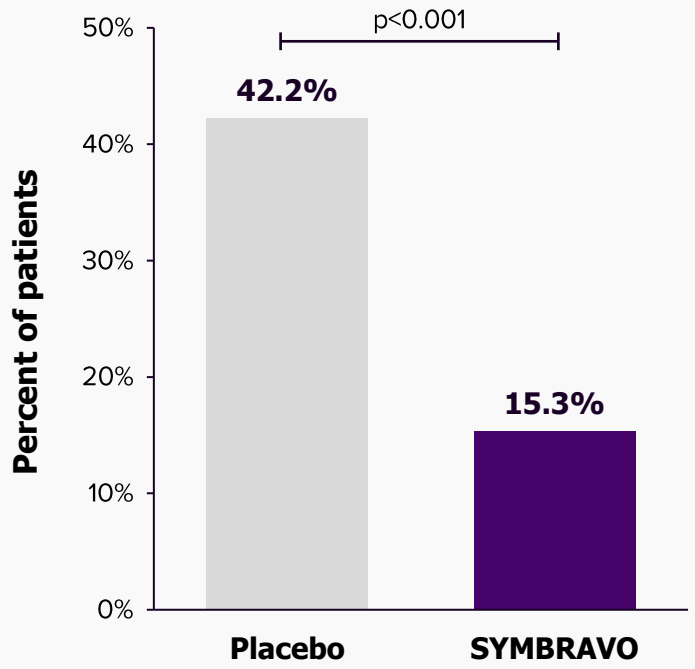
Axsome Therapeutics, Inc. Data on file.

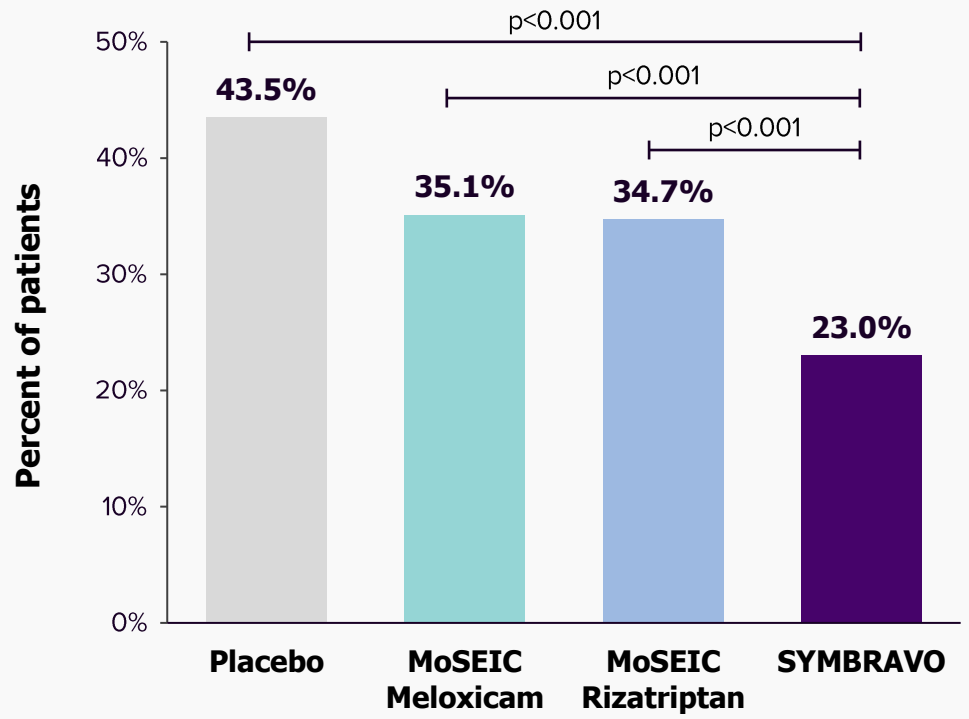
Reduced rescue medication use

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

INTERCEPT



MOMENTUM



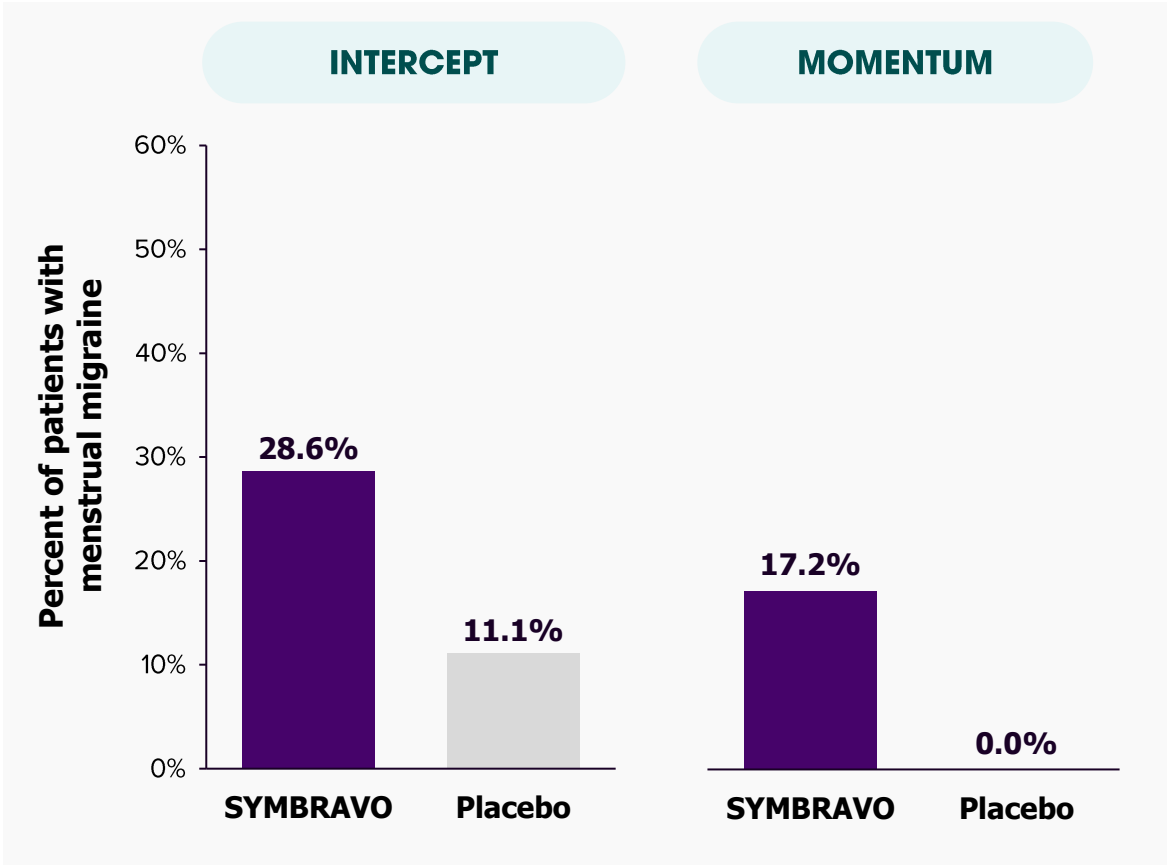
85% and 77% of patients did not require migraine rescue medication within 24 hours after a single dose of SYMBRAVO

Limitation: The analyses of additional endpoints, including the endpoint above, were not tested in hierarchical order or adjusted for multiplicity. Therefore, results cannot be regarded as statistically significant. Axsome Therapeutics, Inc. Data on file.

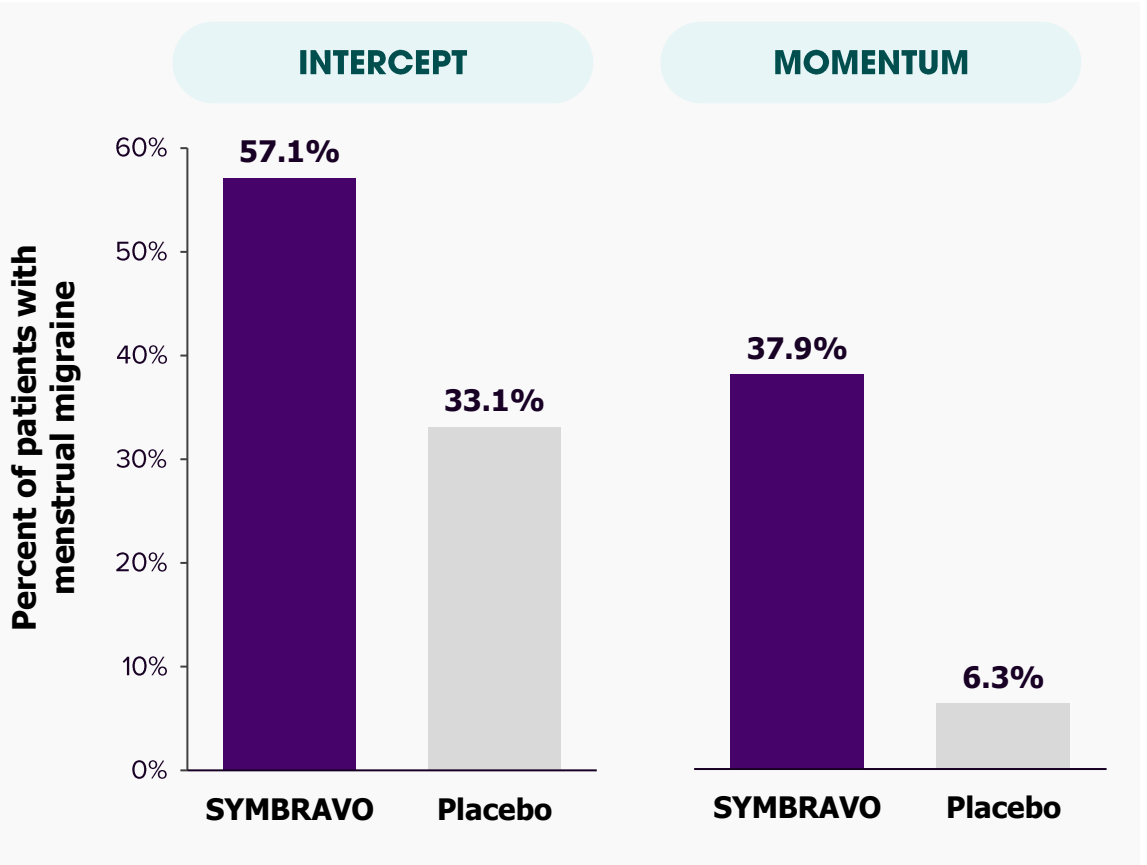
Menstrual migraine subgroup analysis[1]

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

Pain freedom at 2 hours



MBS freedom at 2 hours

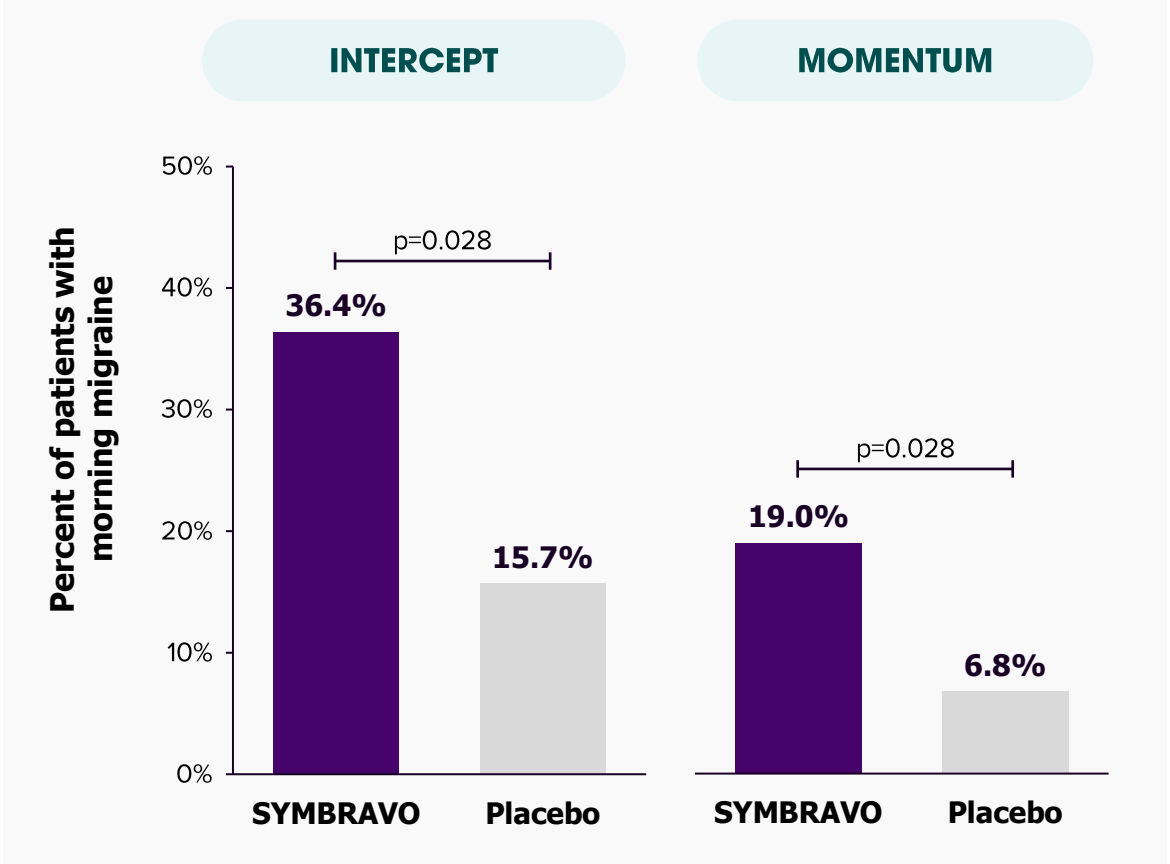


1. Post-hoc analysis (INTERCEPT: SYMBRAVO n=7, placebo n=9; MOMENTUM: SYMBRAVO n=29, placebo n=16); Axsome Therapeutics, Inc. Data on file.

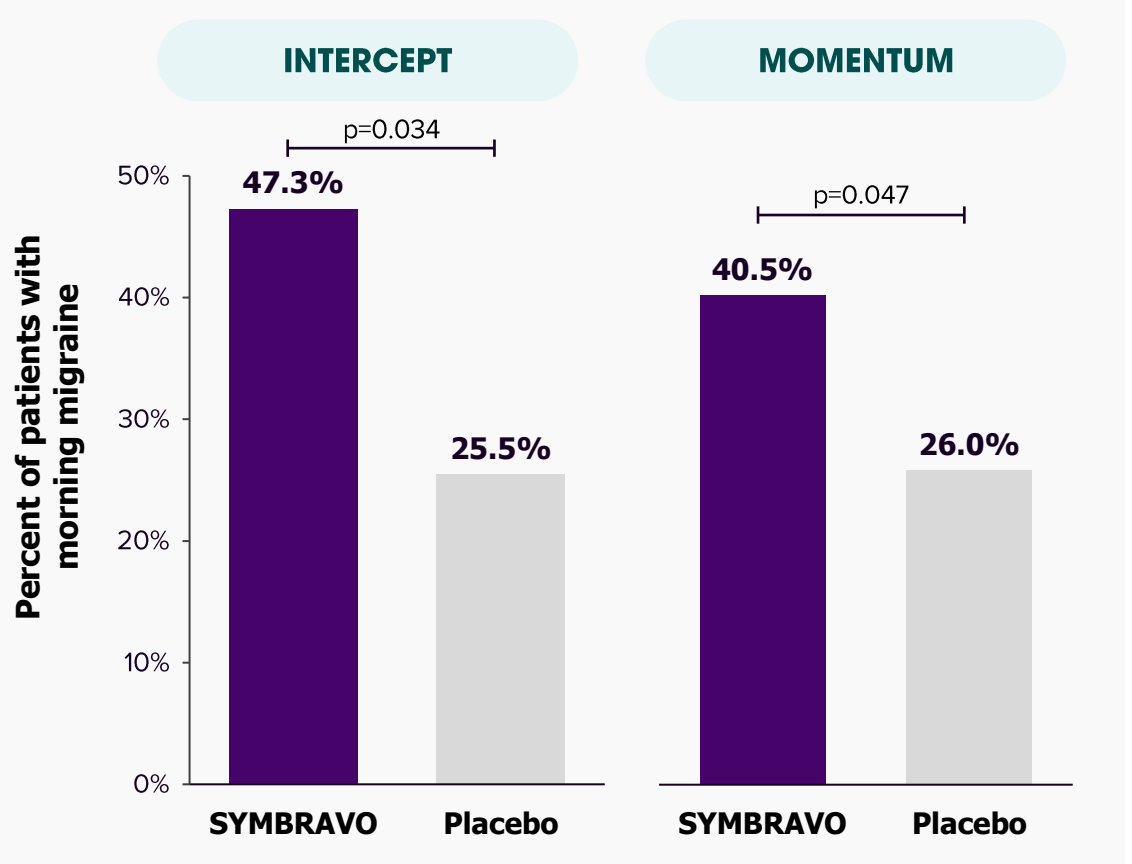
Morning migraine subgroup analysis[1]

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

Pain freedom at 2 hours



MBS freedom at 2 hours



1. Post-hoc analysis (INTERCEPT: SYMBRAVO n=55, placebo n=51; MOMENTUM: SYMBRAVO n=158, placebo n=73); Axsome Therapeutics, Inc. Data on file.

Safety and tolerability summary

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

SYMBRAVO was well tolerated in patients with mild, moderate, and severe migraine pain:

Low incidence of adverse events

Overall TEAE rates were *lower* for SYMBRAVO compared to rizatriptan and meloxicam

No discontinuations due to adverse events

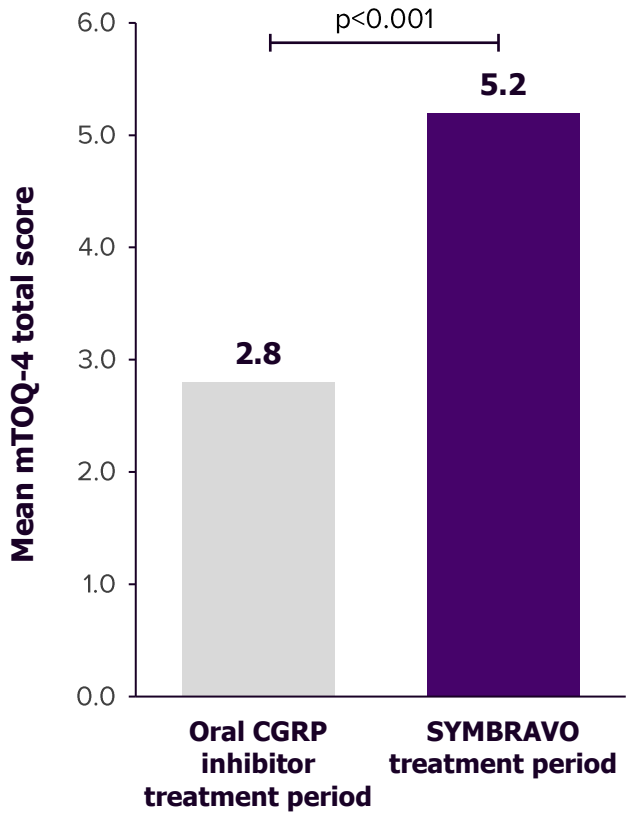
No adverse events led to discontinuation of SYMBRAVO in early intervention or harder-to-treat migraine patients

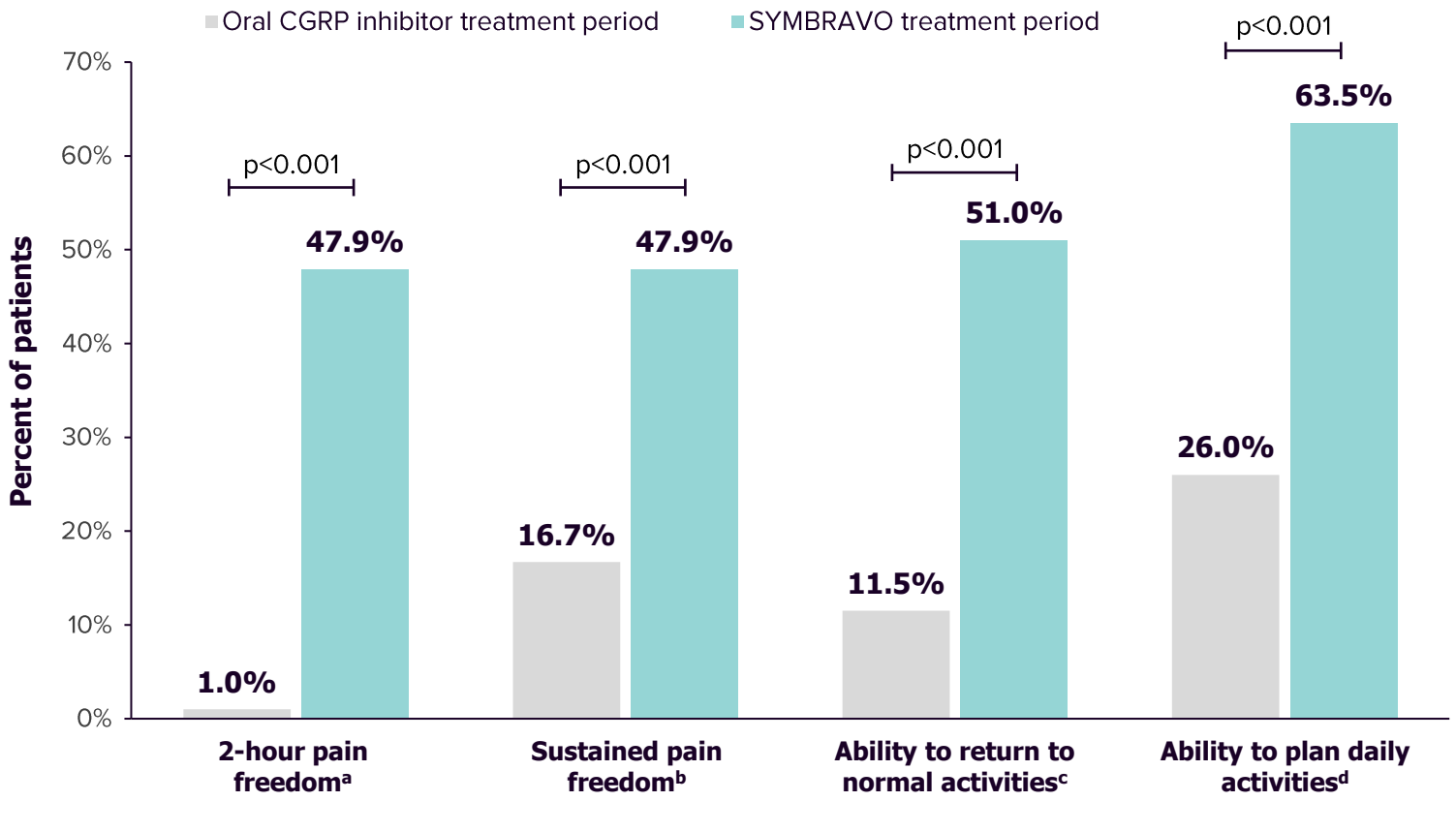
Statistically significantly greater migraine treatment response compared to prior oral CGRP inhibitors

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

EMERGE

Clinical response on individual mTOQ-4 item scores[1]





1. Clinical response defined as reported half the time or more; [a]mTOQ-4 Item 2: *"After taking your migraine medication, are you pain free within 2 hours for most attacks?"*; [b]mTOQ-4 Item 3: *"Does one dose of your migraine medication usually relieve your headache and keep it away for at least 24 hours?"*; [c]mTOQ-4 Item 1: *"Are you able to quickly return to your normal activities after taking your migraine medication?"*; [d]mTOQ-4 Item 4: *"Are you comfortable enough with your migraine medication to be able to plan your daily activities?"* Axsome Therapeutics, Inc. Data on file.

SYMBRAVO: Key takeaways

SYMBRAVO®
(meloxicam and rizatriptan)
20 mg/10 mg tablets

Migraine pathophysiology involves ***multiple, interrelated mechanisms*** not adequately addressed by most available treatments

Patient outcomes are marked by ***high dissatisfaction*** due to limited efficacy and/or burdensome side effects

SYMBRAVO is a ***novel multi-mechanistic medicine*** for the acute treatment of migraine

SYMBRAVO demonstrated ***rapid and durable efficacy*** across a variety of migraine settings

New subgroup analyses further support potential benefits in patients with ***menstrual and morning migraine***

New frontiers in brain health

		Indication	Innovation	Development stage	Peak sales
Psychiatry	Auvelity® (dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg	**Major depressive disorder**	First-in-class MOA, FDA Breakthrough therapy	In-market	**$1-$3B**
	AXS-05 *(dextromethorphan-bupropion)* NMDA antagonist, sigma-1 agonist, and aminoketone CYP2D6 inhibitor	**Alzheimer's disease agitation**	First-in-class MOA, FDA Breakthrough therapy	NDA-stage	**$1.5-$3B**
		Smoking cessation	First-in-class MOA	Phase 3	**$0.5-$1B**
	Solriamfetol DNRI , TAAR1 agonist, 5-HT_{1A} agonist	**ADHD**	Novel MOA	Phase 3	**$1-$3B**
		MDD with EDS	Novel MOA, precision-driven targeting	Phase 3	**$1-$1.5B**
		Binge eating disorder	Novel indication	Phase 3	**$0.5-$1B**
Neurology	SUNOSI (solriamfetol) (IV)	**EDS in narcolepsy or OSA**	First-in-class, best-in-class MOA	In-market	**$0.3-$0.5B**
	SYMBRAVO® (meloxicam and rizatriptan) 20 mg/10 mg tablets	**Migraine**	MoSEIC™ technology-enabled NCE	In-market	**$0.5-$1B**
	AXS-12 *(reboxetine)* Highly selective NRI, dopamine mod.	**Narcolepsy**	Novel MOA, pro-cognitive	NDA-stage	**$0.5-$1B**
	AXS-14 *(esreboxetine)* [S,S]-enantiomer of AXS-12	**Fibromyalgia**	Best-in-class MOA, addresses fatigue	Phase 3	**$0.5-$1B**
	Solriamfetol DNRI , TAAR1 agonist, 5-HT_{1A} agonist	**Shift work disorder**	Best-in-class MOA	Phase 3	**$0.3-$0.5B**

Advancing novel medicines with the potential to deliver significant long-term value to patients and shareholders

>$16B peak sales potential

>150M patients

>600 issued patents extending out to early 2040s

Thank you

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