FDA Approval of AUVELITY® in Agitation Associated with Dementia due to Alzheimer's Disease

Investor Overview

May 1, 2026

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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Today's agenda

Introduction	**Mark Jacobson, MA** Chief Operating Officer
Opening Remarks	**Herriot Tabuteau, MD** Chief Executive Officer
Commercial Overview	**Ari Maizel** Chief Commercial Officer
Alzheimer's Disease Agitation	**Jeffrey Cummings, MD, ScD** Chambers-Grundy Professor of Brain Sciences, UNLV Kirk Kerkorian School of Medicine
Closing Remarks	**Herriot Tabuteau, MD**
Q&A	**Dr. Cummings and Axsome Management**

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Opening Remarks

Herriot Tabuteau, MD

Founder and Chief Executive Officer

Our Mission

Develop and deliver
transformative medicines
to improve the brain health
of millions of individuals

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NEW APPROVED INDICATION

AUVELITY®

For Agitation Associated with Dementia due to Alzheimer's Disease

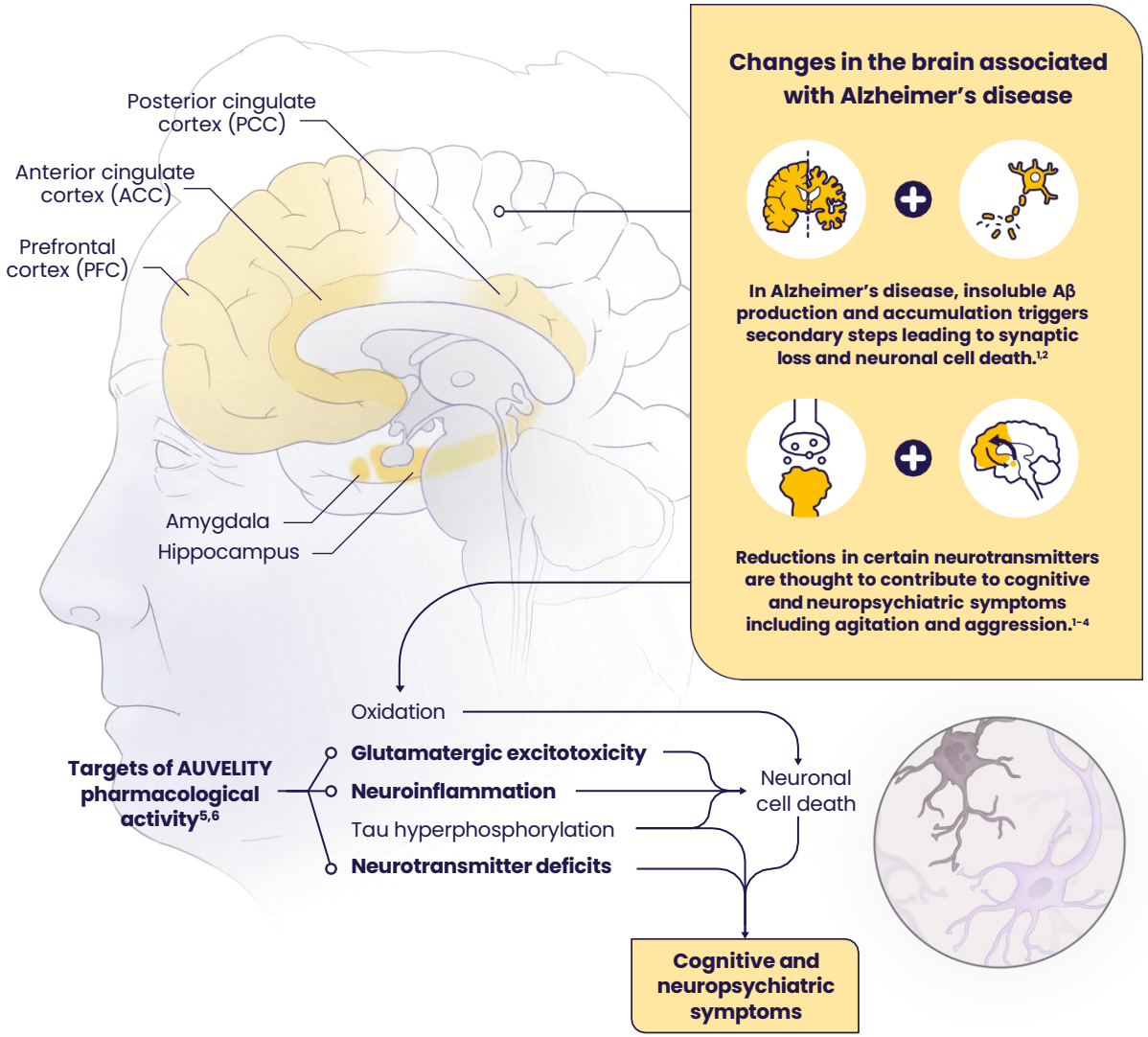
A **first-in-class** treatment that targets NMDA and sigma-1 receptors

Mechanism of 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]

AUVELITY targets the NMDA and sigma-1 receptors believed to *modulate the function* of neurotransmitters implicated in Alzheimer's disease[1-4]



1. Cummings JL. 2004; 2. Querfurth HW, LaFerla FM 2010; 3. Porsteinsson AP, Antonsdottir IM. 2017; 4. Rosenberg PB, Nowrangi MA, Lyketsos CG. 2015; 5. Stahl SM. 2019; 6. Cheng W, et al. 2015

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First-in-class treatment for agitation associated with Alzheimer's disease

Efficacy demonstrated in short-term and long-term studies

- Only approved treatment for agitation associated with dementia due to Alzheimer's disease demonstrating substantial symptom improvement and statistically significantly longer time to relapse

Distinct safety and tolerability profile

- Most common adverse reactions† were dizziness and dyspepsia
- 1.3% of patients treated with AUVELITY discontinued due to an adverse event, the same rate as placebo
- No new boxed warning

Addressing a serious unmet medical need

- Approved through Priority Review following Breakthrough Therapy designation

NMDA = N-methyl D-aspartate
†Defined as ≥5% and more than twice placebo

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AUVELITY highlights of prescribing information

Updates for new indication highlighted in yellow

INDICATIONS AND USAGE

AUVELITY is a combination of dextromethorphan, an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone and CYP450 2D6 inhibitor, indicated for:

- the treatment of major depressive disorder (MDD) in adults (1.1)
- the treatment of agitation associated with dementia due to Alzheimer's disease (1.2)

Limitations of Use: AUVELITY is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease (1.2).

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.1)]*.

AUVELITY is not approved for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

WARNINGS AND PRECAUTIONS

- Seizure: Risk is dose-related. Discontinue if seizure occurs. (4, 5.2)
- Increased Blood Pressure and Hypertension: AUVELITY can increase blood pressure and cause hypertension. Assess blood pressure before initiating treatment and monitor periodically during treatment. (5.3)
- Activation of Mania or Hypomania: Screen patients for bipolar disorder. (5.4)
- Psychosis and Other Neuropsychiatric Reactions: Instruct patients to contact a healthcare provider if such reactions occur. (5.5)
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.6)
- Dizziness: AUVELITY may cause dizziness. Take precautions to reduce falls and use caution when operating machinery. (5.7)
- Serotonin Syndrome: Use of AUVELITY with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk. Discontinue if occurs. (5.8, 7.1)
- Embryo-fetal Toxicity: May cause fetal harm. Advise pregnant females of the potential risk to a fetus. Discontinue treatment in pregnant females and use alternative treatment for females who are planning to become pregnant. (5.9, 8.1, 8.3)
- Hyponatremia: Can occur in association with SIADH. (5.10)

ADVERSE REACTIONS

- MDD: Most common adverse reactions (≥5% and more than twice as frequently as placebo): dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis. (6.1)
- Agitation associated with dementia due to Alzheimer's disease: Most common adverse reactions (≥5% and more than twice as frequently as placebo): dizziness and dyspepsia. (6.1)

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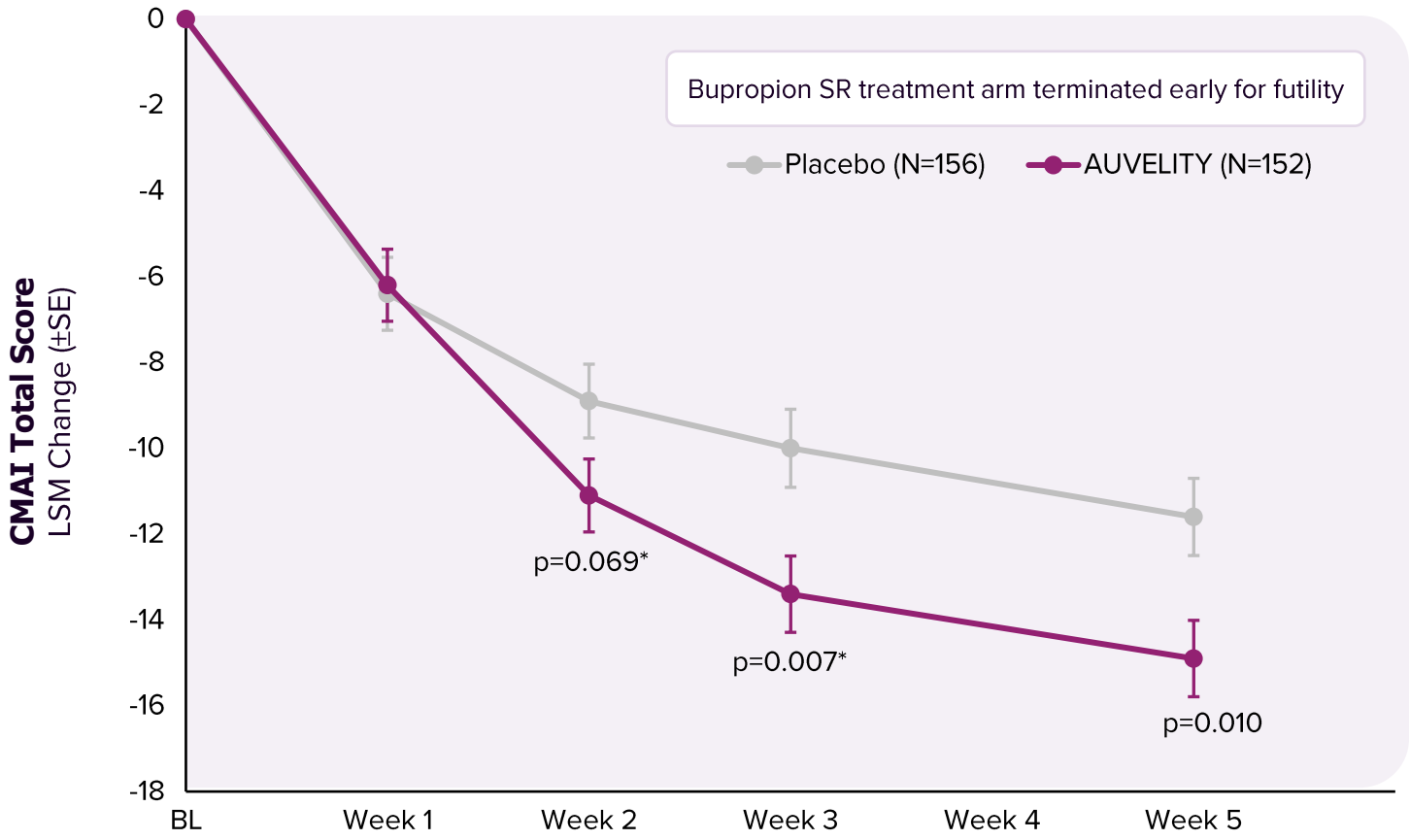
AUVELITY demonstrated significant improvement in agitation symptoms

ADVANCE-1[a,b]



Primary endpoint: Change from baseline in CMAI total score at Week 5

14.9-point
reduction in the CMAI total score at Week 5 with AUVELITY

vs

11.6-point
reduction with placebo

p=0.010

A statistically significantly greater proportion of patients receiving AUVELITY achieved a clinical response on the mADCS-CGIC (key secondary)

ⓘ The CMAI is a validated caregiver-rated scale that measures the frequency of agitated behaviors

CMAI = Cohen-Mansfield Agitation Inventory; LSM = least-squares mean; SE = standard error; SR = sustained release
a. Efficacy analysis was conducted in the Modified Intent-to-Treat population, defined as all patients who received ≥1 dose of study medication and ≥1 post-baseline efficacy assessment;
b. p-values shown for AUVELITY vs. placebo; *Not prespecified endpoints, p-values are nominal; c. Bupropion arm discontinued early for futility
Axsome Therapeutics, Inc. Data on file.

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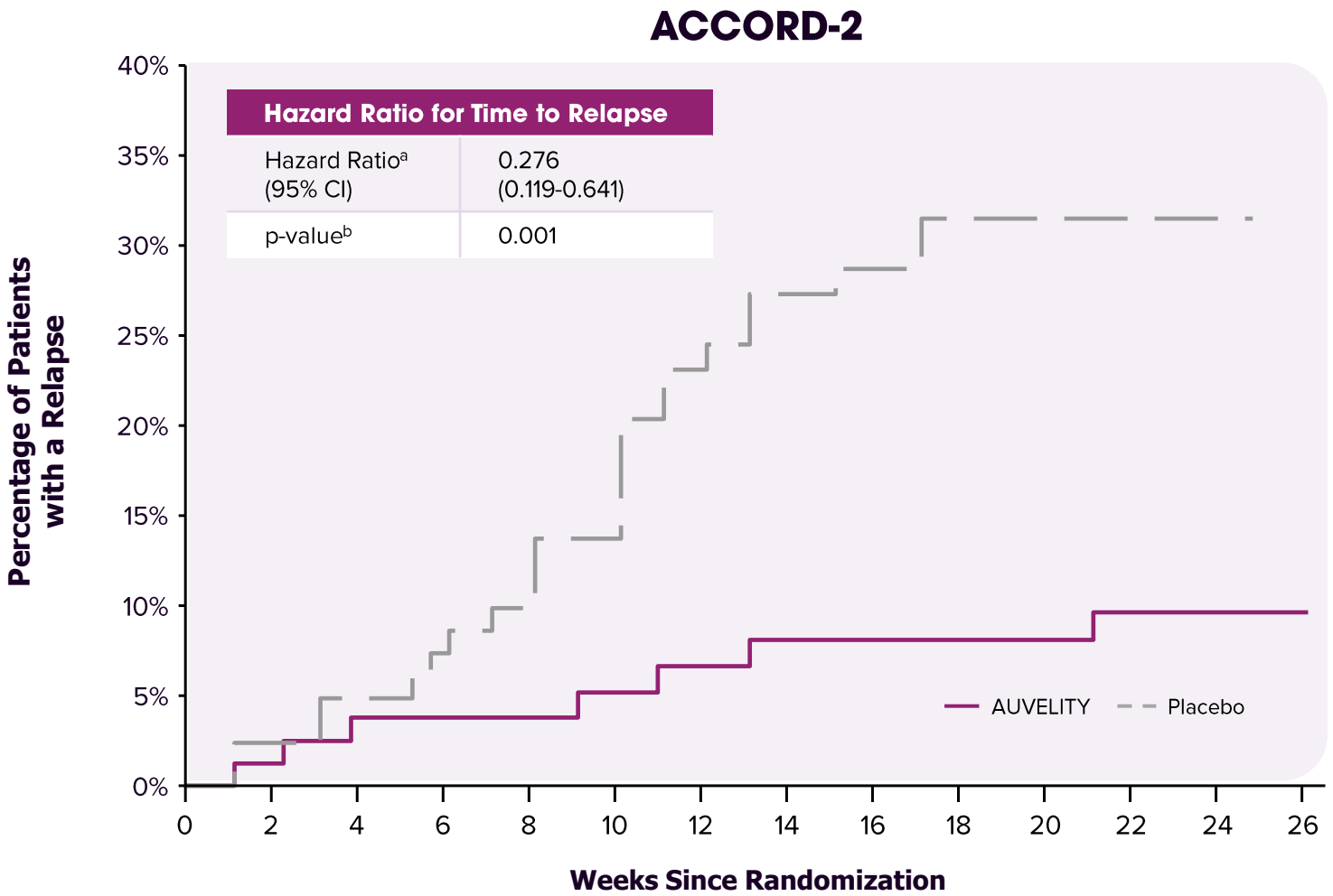
AUVELITY demonstrated sustained efficacy and relapse prevention in a long-term study



Primary endpoint: Time from randomization to relapse of agitation

72.4%
reduction in relapse risk with AUVELITY vs placebo[a]

8.4%
of patients relapsed with AUVELITY

vs

28.6%
of patients relapsed with placebo

a. Hazard ratio estimated using a Cox proportional hazards model; b. p-value based on a log-rank test

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Commercial Overview

Ari Maizel

Chief Commercial Officer

Opportunity to advance care for a critically underserved neuropsychiatric condition

Alzheimer's disease agitation

>5M People in the U.S. living with Alzheimer's disease agitation

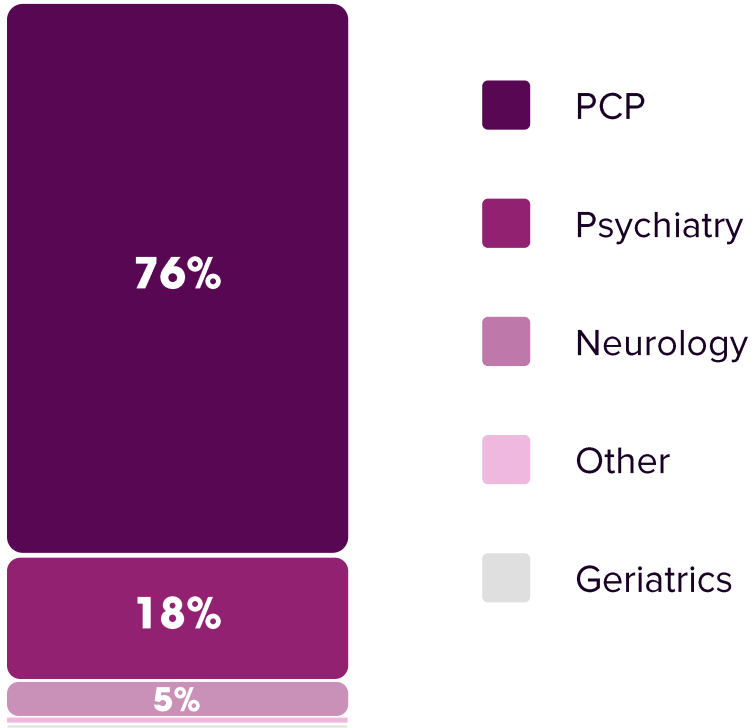
~50% Patients treated with a pharmacotherapy[1]

1 Previously approved treatment

40%
Long-term care

60%
Community-dwelling patients

Prescriber mix



PCP = primary care provider
1. Symphony Health Claims

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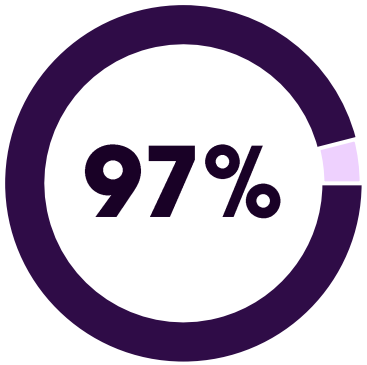
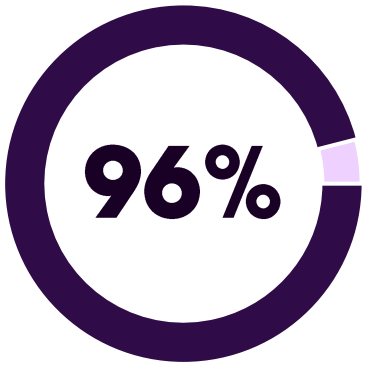
A large survey of Alzheimer's care partners underscores the burden associated with agitation symptoms

A survey of 751 care partners* sponsored by Axsome Therapeutics in partnership with a leading polling and research survey firm highlighted the challenges in the **identification, treatment, and management** of agitation associated with Alzheimer's disease

*Includes spouses, partners, children, grandchildren, family members, and friends



Say agitation has a **negative impact** on their loved one's quality of life



Agree their loved one seems more like themselves when agitation is **under control**

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Expanding AUVELITY's reach into Alzheimer's disease agitation

FIELD FORCE EXPANSION

~630 Sales representatives

~68K HCP targets treating MDD and Alzheimer's disease agitation

STRONG MARKET ACCESS

100% Medicare and Medicaid lives covered

78% Commercial lives covered

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Launch readiness

- Educational efforts across community and long-term care settings
- Broad insurance coverage and comprehensive patient support
- Commercial launch anticipated in approximately one month

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Alzheimer's Disease Agitation

Jeffrey Cummings, MD, ScD

Chambers-Grundy Professor of Brain Sciences,

UNLV Kirk Kerkorian School of Medicine

Agitation is a common behavioral symptom that may present across multiple stages of Alzheimer's disease

Agitation encompasses three broadly defined symptom domains including both non-aggressive and aggressive behaviors[1,2]

Excessive motor activity

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

Verbal aggression

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

Physical aggression

- Grabbing
- Resisting
- Pushing
- Hitting
- Kicking
- Scratching
- Biting
- Throwing objects
- Tearing things
- Destroying property

Prevalence of agitation across AD severity[3]:

- **56%** Mild
- **75%** Moderate-to-severe
- **68%** Severe

1. Cummings J, et al. *Int Psychogeriatr.* 2015; 2. Sano M, et al. *Int Psychogeriatr.* 2023; 3. Halpern R, et al. *Int J Geriatr Psychiatry* 2018

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

Cohen-Mansfield Agitation Inventory (CMAI)[1]

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

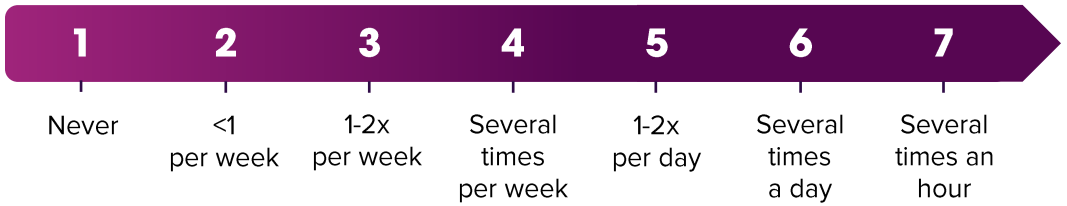
- Cursing
- Making strange noises
- Screaming
- Making verbal sexual advances

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

IPA = International Psychogeriatric Association

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

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Agitation is among the most prevalent and distressing neuropsychiatric symptom of Alzheimer's disease

>7M

people in the U.S. live with Alzheimer's disease, projected to double in the coming decades[1]

Up to

76%

of individuals with Alzheimer's disease experience agitation during the course of their illness[1]

Alzheimer's disease agitation is associated with serious negative patient outcomes...

- Accelerated disease progression[2,3]
- Functional decline[2,3]
- Increased and earlier institutionalization[4,5]
- Increased fall and mortality risk[2,6,7]

...And a significant burden on caregivers and the healthcare system

Significantly more caregiving hours per week and greater healthcare utilization compared to patients without agitation[4,7-10]

Agitation is a leading cause of long-term care placement in Alzheimer's disease

1. 2026 Alzheimer's Disease Facts and Figures. 2. Peters ME, et al. 2015; 3. Kociolek AJ, et al. 2023; 4. Porsteinsson AP, Antonsdottir IM. 2017; 5. Cloutier M, et al. 2019; 6. Jones E, et al. 2021; 7. Grossberg G, et al. 2024.

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Alzheimer's disease agitation treatment landscape

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]

Historical pharmacologic treatments have been primarily off-label medications:

- Typical and atypical antipsychotics, antidepressants, benzodiazepines, antiepileptics
- One approved atypical antipsychotic (brexpiprazole)
- ~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 with atypical antipsychotics
- Modest efficacy

AUVELITY is a new FDA-approved treatment option for Alzheimer's disease agitation

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1. 2026 Alzheimer's Disease Facts and Figures; 2. Trachtenberg et al. 2002; 3. Veeva Compass Claims Data.

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AUVELITY in Alzheimer's disease agitation conclusions

1 Unmet Need

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

2 Novel Mechanism

- **AUVELITY** targets NMDA and sigma-1 receptors that modulate glutamatergic pathways implicated in Alzheimer's disease agitation

3 Clinical Results

AUVELITY studies showed:

- Significant reduction in agitation
- Safe and well tolerated
- Patient and clinical impression of change converged (CMAI and mADCS-CGIC), supporting validity
- Onset of action was rapid and sustained

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Closing Remarks

Herriot Tabuteau, MD

Chief Executive Officer

A singular CNS platform

3
marketed products

Auvelity®
(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

SUNOSI®
(solriamfetol) CIV

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

4
approved indications

MDD	**21M+**
AADAD	**5M+**
EDS in OSA or narcolepsy	**22M+**
Migraine	**39M+**

Singular
pipeline

6 novel product candidates

10 high-unmet-need indications

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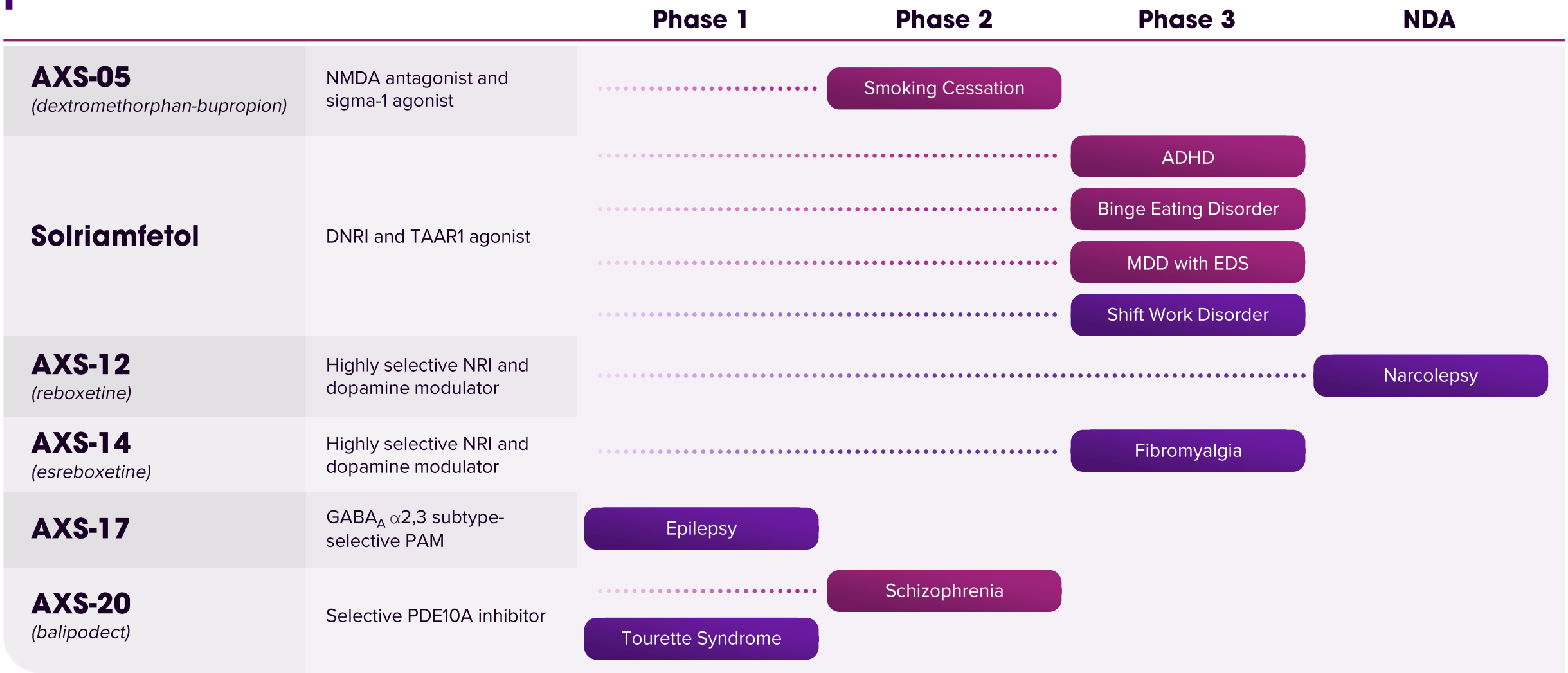
Psychiatry | Neurology

Leading neuroscience pipeline with deep stratification



NMDA = N-methyl-D-aspartate; CYP2D6 = Cytochrome P450 Family 2 Subfamily D Member 6; DNRI = Dopamine-norepinephrine reuptake inhibitor; TAAR1 = Trace amine-associated receptor 1; 5-HT = 5-Hydroxytryptamine; NRI = Norepinephrine reuptake inhibitor; GABA = gamma-aminobutyric acid

Please see full Prescribing Information for AUVELITY, SUNOSI, and SYMBRAVO at www.AUVELITY.com, www.SUNOSI.com, and www.SYMBRAVO.com, respectively.

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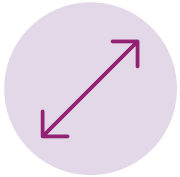
Advancing the frontiers of brain health

Broad commercial portfolio

Three innovative medicines improving patient outcomes and driving durable growth



Expanding AUVELITY

Second approved indication expanding reach and accelerating growth

Industry-leading CNS pipeline

Potential first-in-class, best-in-class treatments across ten serious CNS conditions

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