UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 30, 2024

Axsome Therapeutics, Inc.

(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-37635**	**45-4241907**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

One World Trade Center, 22nd Floor **New York, New York**	**10007**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (212) 332-3241

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, Par Value $0.0001 Per Share	AXSM	Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On December 30, 2024, Axsome Therapeutics, Inc. (the "Company") issued a press release announcing the results of its ADVANCE-2 and ACCORD-2 trials of the Company's AXS-05 product candidate for the treatment of Alzheimer's disease agitation. The Company will host a conference call at 8:00 a.m. ET on December 30, 2024 to discuss the topline results of these trials.

The full text of the press release is filed as Exhibit 99.1 hereto and is incorporated herein by reference. A copy of the presentation that the Company will use in connection with the conference call is filed as Exhibit 99.2 hereto and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release dated December 30, 2024.
99.2	AXS-05 ADA Presentation.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Axsome Therapeutics, Inc.

Date: December 30, 2024

By: /s/ Herriot Tabuteau, M.D.
Name: Herriot Tabuteau, M.D.
Title: President and Chief Executive Officer

Exhibit 99.1

Axsome Therapeutics Announces Successful Completion and Results of Phase 3 Clinical Program of AXS-05 in Alzheimer's Disease Agitation

ACCORD-2 Phase 3 trial in Alzheimer's disease agitation achieves primary endpoint compared to placebo (p=0.001, time to relapse)

ACCORD-2 Phase 3 trial achieves key secondary endpoint compared to placebo (p=0.001, prevention of relapse of Alzheimer's disease agitation)

AXS-05 reduced worsening of Alzheimer's disease overall compared to placebo in ACCORD-2 Phase 3 trial (p<0.001, CGI-S Alzheimer's disease overall clinical status)

ADVANCE-2 trial did not demonstrate statistical significance on primary endpoint; numerically greater improvements with AXS-05 over placebo (primary and secondary endpoints)

Long-term safety trial completed with required number of patients treated for 6 and 12 months

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

Four completed pivotal, Phase 3, placebo-controlled trials support efficacy and safety of AXS-05 in Alzheimer's disease agitation

The Company plans to submit a New Drug Application (NDA) to the FDA in 2H 2025

Conference call and webcast to take place today at 8:00 AM Eastern

NEW YORK, December 30, 2024 (Globe Newswire) – Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company developing and delivering novel therapies for the management of central nervous system (CNS) disorders, today announced the successful completion of its Phase 3 clinical program evaluating AXS-05 (dextromethorphan-bupropion), a novel, oral, investigational NMDA receptor antagonist, sigma-1 agonist, and aminoketone CYP2D6 inhibitor, in Alzheimer's disease agitation, and results of the ACCORD-2, ADVANCE-2, and long-term safety trials in this indication.

The ACCORD-2 Phase 3 trial achieved the primary endpoint with AXS-05 statistically significantly delaying the time to relapse of agitation, assessed by the Cohen-Mansfield Agitation Inventory (CMAI) total score, in patients with Alzheimer's disease compared to placebo (hazard ratio for time to relapse of 0.276, p=0.001), demonstrating a 3.6-fold lower risk of relapse compared to placebo. AXS-05 also met the key secondary endpoint (relapse prevention, p=0.001). Further, AXS-05 reduced worsening for overall Alzheimer's disease severity compared to placebo, as assessed by the Clinical Global Impression of Severity (CGI-S) for Alzheimer's disease (p<0.001).

The ADVANCE-2 Phase 3 trial did not demonstrate statistical significance for the primary endpoint, change in the CMAI total score from baseline to Week 5 (CMAI reductions of 13.8 and 12.6 points for AXS-05 and placebo, respectively). However, results for the primary and nearly all secondary endpoints numerically favored AXS-05 over placebo.

AXS-05 was safe and well tolerated in both controlled studies. The long-term safety and tolerability of AXS-05 was also evaluated in more than 300 subjects treated for at least 6 months and more than 100 subjects treated for at least 12 months. In the controlled and long-term studies in subjects with Alzheimer's disease, AXS-05 was not associated with increased risk of falls, cognitive decline, or sedation. In the clinical program for AXS-05 in Alzheimer's disease agitation, there have been no deaths in subjects receiving AXS-05.

AXS-05 has now demonstrated statistically significant efficacy compared to placebo in three completed pivotal Phase 3 trials (ADVANCE-1, ACCORD-1 and ACCORD-2), with supportive efficacy and controlled safety results in a fourth trial (ADVANCE-2). Axsome plans to submit an NDA for AXS-05 in Alzheimer's disease agitation to the FDA in the second half of 2025, based on the efficacy and safety data from the above controlled and long-term studies. AXS-05 has been granted Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation.

Jeffrey Cummings, MD, ScD, Vice Chair of Research, UNLV Department of Brain Health commented, "Agitation is one of the most troubling and consequential aspects of Alzheimer's disease, poses significant challenges to both the patient and their family, and represents a high unmet need. The robust, clinically meaningful efficacy results of the ACCORD-2 trial are consistent with the statistically significant results of the previously completed ADVANCE-1 and ACCORD-1 Phase 3 trials of AXS-05. The improvement in overall Alzheimer's disease severity with AXS-05 in the ACCORD-2 trial is noteworthy. Importantly, short and long-term treatment with AXS-05 was well tolerated and not associated with increased mortality, risk of falls, sedation, or cognitive decline. Taken together, results from this comprehensive Phase 3 program encompassing distinct clinical trial designs strongly support the potential for AXS-05 to become an important treatment for patients living with Alzheimer's disease agitation."

Herriot Tabuteau, MD, CEO of Axsome Therapeutics, added, "We are very pleased with the successful completion of the planned Phase 3 clinical trial program of AXS-05 in the treatment of Alzheimer's disease agitation. With the strong results of the ACCORD-2 trial, AXS-05 has now demonstrated substantial and statistically significant improvements in Alzheimer's disease agitation across three pivotal, Phase 3, placebo-controlled trials, underscoring its potential to provide meaningful benefit to patients living with this condition and their families. The improvements in the AXS-05 arm relative to placebo in ADVANCE-2 did not reach statistical significance. However, we are pleased with the very positive controlled safety data from this trial which will be an essential part of our planned NDA submission of AXS-05 in Alzheimer's disease agitation, which is targeted for the second half of 2025."

Summary of Topline Results of the ACCORD-2 Phase 3 Trial

ACCORD-2 was a double-blind, placebo-controlled, randomized withdrawal trial of AXS-05 in Alzheimer's disease patients with agitation, consisting of an open-label AXS-05 treatment period, and a randomized, double-blind treatment period. Patients who achieved a sustained clinical response with open-label AXS-05 were then randomized into the double-blind treatment period to either continue on AXS-05 or to switch to placebo.

Open-Label AXS-05 Treatment Period

A total of 295 patients were treated with open-label AXS-05 for up to 12 months and assessed for efficacy. The mean CMAI total score was 73.3 at baseline.

- Treatment with AXS-05 was associated with a mean reduction from baseline in the CMAI total score of 20.4 points at Week 6, representing a 46% reduction from the mean baseline score.
- Clinical response on the CMAI (defined as ≥30% reduction from baseline) after treatment with AXS-05 was achieved by 69% of patients at Week 6, after treatment with AXS-05.
- Improvement in Alzheimer's disease agitation, assessed using the clinician rated modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC), was achieved by 78% of patients at Week 6, after treatment with AXS-05.
- Improvement in Alzheimer's disease agitation, assessed using the caregiver rated Patient Global Impression of Change (PGI-C), was achieved by 71% of patients at Week 4, and 78% of patients at Week 8, after treatment with AXS-05.
- Of the patients treated for at least 8 weeks, 70% experienced a sustained clinical response and were randomized in the double-blind period.

Double-Blind Randomized Period

A total of 167 patients were randomized, 83 to continued treatment with AXS-05, and 84 switched to placebo. The mean CMAI total scores at randomization were 44.3 and 45.4 for the AXS-05 and placebo groups respectively.

- AXS-05 met the primary endpoint by substantially and statistically significantly delaying the time to relapse of Alzheimer's disease agitation as compared to placebo (hazard ratio for time to relapse of 0.276, p=0.001), demonstrating a 3.6-fold lower risk of relapse compared to placebo.
- AXS-05 met the key secondary endpoint by substantially and statistically significantly preventing relapse of Alzheimer's disease agitation as compared to placebo, with 8.4% of AXS-05 patients relapsing versus 28.6% of patients switched to placebo (p=0.001).
- AXS-05 substantially and statistically significantly prevented worsening of severity of Alzheimer's disease agitation as compared to placebo, with 20.5% of AXS-05 patients worsening on the CGI-S for agitation versus 41.7% of patients switched to placebo (p=0.004).
- AXS-05 substantially and statistically significantly prevented worsening of severity of Alzheimer's disease overall as compared to placebo, with 13.3% of AXS-05 patients worsening on the CGI-S for Alzheimer's disease overall clinical status versus 39.3% of patients switched to placebo (p<0.001).

The overall rates of adverse events in the double-blind period were 29.3% in the AXS-05 group and 32.1% in the placebo group, with no individual adverse events occurring in more than 3.7% of subjects. Two subjects (2.4%) in the AXS-05 group experienced falls, only one which was deemed related to study medication. There were two serious adverse events in the double-blind period (cellulitis and urinary retention) both of which occurred in the placebo group. Discontinuations in the double-blind period due to adverse events were low (0% for AXS-05 and 1.2% for placebo).

There were no deaths in the ACCORD-2 trial, and AXS-05 was not associated with sedation or cognitive decline as assessed by the Mini-Mental State Examination (MMSE).

Summary of Topline Results of the ADVANCE-2 Phase 3 Trial

The ADVANCE-2 trial was a double-blind, placebo-controlled, parallel group trial of AXS-05 in Alzheimer's disease patients with agitation. A total of 408 patients were randomized in a 1:1 ratio to treatment with AXS-05 or placebo, for 5 weeks.

- The study did not demonstrate statistical significance for the primary endpoint, change in the CMAI total score from baseline to Week 5 (CMAI reductions of 13.8 and 12.6 points for AXS-05 and placebo, respectively).
- Results of the primary endpoint and almost all secondary endpoints numerically favored AXS-05 over the placebo group.

The overall rates of adverse event in ADVANCE-2 were 26.0% in the AXS-05 group and 21.6% in the placebo group. The most common adverse events were dizziness (5.9% for AXS-05 and 1.5% for placebo), and headache (4.4% for AXS-05 and 3.4% placebo). One subject (0.5%) each in the AXS-05 and placebo groups experienced falls, which was deemed not related to study medication for the subject in the AXS-05 group. Two subjects in the AXS-05 group reported three serious adverse events, none of which were deemed related to study drug (asthenia, urinary tract infection, cerebrovascular accident). Discontinuation due to adverse events were low (1.5% for AXS-05 and 0% for placebo).

In the ADVANCE-2 trial, there were no deaths and AXS-05 was not associated with sedation or cognitive decline as assessed by the MMSE.

Summary of Long-Term Safety

A total of 456 subjects were treated for up to 12 months with AXS-05 in the long-term open-label safety trial. AXS-05 was well tolerated with long-term dosing, with a safety profile consistent with the short-term efficacy and safety trials and no new safety signals identified.

The overall rate of adverse events during the up to 12-month treatment period was 39.9%, with headache (5.5%) being the only adverse event occurring in ≥5% of subjects. The rate of falls over the up to 12-month treatment period was 3.1%, with only 0.2% deemed related to study medication. The rate of serious adverse events during the up to 12-month treatment period was 2.6%, none of which were deemed related to study drug. Discontinuations due to adverse events with long-term dosing were low (0.7%).

There were no deaths and AXS-05 was not associated with sedation or cognitive decline as assessed by the MMSE.

Overall Phase 3 Clinical Development Program

The comprehensive clinical development program of AXS-05 in Alzheimer's disease agitation includes four completed pivotal, Phase 3, placebo-controlled trials that support the efficacy of AXS-05 in this indication:

- ADVANCE-1 – achieved primary endpoint (p=0.010)
- ADVANCE-2 – primary endpoint not statistically significant
- ACCORD-1 – achieved primary endpoint (p=0.014)
- ACCORD-2 – achieved primary endpoint (p=0.001)

The long-term safety of AXS-05 in Alzheimer's disease agitation has been demonstrated in over 300 patients treated for at least 6 months, and over 100 patients treated for at least 12 months.

Axsome plans to submit an NDA for AXS-05 in Alzheimer's disease agitation to the FDA in the second half of 2025, based on the efficacy and safety data from these studies.

AXS-05 was granted Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation in June 2020 based on positive results from the pivotal ADVANCE-1 trial. Breakthrough Therapy designation is granted to potentially expedite development and review timelines for a promising investigational medicine when preliminary clinical evidence indicates it may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies for a serious or life-threatening condition.

Conference Call Information

Axsome will host a conference call and webcast today at 8:00 a.m. Eastern Time to discuss the topline results of the ADVANCE-2 and ACCORD-2 Phase 3 trials of AXS-05 in Alzheimer's disease agitation. Dr. Jeffrey Cummings, Vice Chair of Research, UNLV Department of Brain Health, will join the call and will be available to answer questions during the Q&A session. To participate in the live conference call, please dial (877) 405-1239 (toll-free domestic) or +1 (201) 389-0851 (international). A live webcast of the conference call can be access on the "Webcasts & Presentations" page of the "Investors" section of the Company's website at axsome.com. A replay of the conference call will be available for approximately 30 days following the live event.

About the ADVANCE-2 Trial

ADVANCE-2 (Addressing Dementia via Agitation-Centered Evaluation 2) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, 5-week parallel-group trial. The primary endpoint was the change from baseline in the CMAI total score at Week 5. The minimum score on the CMAI is 29, corresponding to the total absence of symptoms, with higher scores corresponding to greater agitation.

A total of 408 patients with a diagnosis of probable Alzheimer's disease (AD) and clinically meaningful agitation associated with their AD were enrolled in the trial. Patients were randomized 1:1 to receive AXS-05 (dextromethorphan/bupropion, dose escalated from 30 mg/105 mg once daily to 45 mg/105 mg twice daily) or matching placebo for 5 weeks.

About the ACCORD-2 Trial

ACCORD-2 (Assessing Clinical Outcomes in Alzheimer's Disease Agitation 2) was a multicenter Phase 3 trial consisting of an open-label treatment period followed by a 26-week, double-blind, placebo-controlled, randomized withdrawal period. The primary endpoint was the time from randomization to relapse of AD agitation calculated by Kaplan-Meier estimates and the hazard ratio. The key secondary endpoint was the percentage of patients who relapsed compared to placebo.

A total of 167 patients, who rolled over from the open-label extension trial of AXS-05, experienced a sustained clinical response with AXS-05 and were 1:1 randomized to continue AXS-05 (n=83) or to switch to placebo (n=84). Treatment was continued until either a relapse of agitation or the end of the 26-week double-blind period, whichever occurred first. The mean CMAI total score at baseline study entry was 73.3. The mean CMAI total scores at randomization for the AXS-05 and placebo groups were 44.3 and 45.4, respectively.

About Alzheimer's Disease Agitation

Alzheimer's disease (AD) is the most common form of dementia, affecting approximately 7 million people in the United States.[1] Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, verbal and physical aggressiveness, disruptive irritability, and disinhibition.[1,2] AD agitation has been associated with accelerated cognitive decline, increased caregiver burden, earlier nursing home placement, and increased mortality.[3]

About AXS-05

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 agonist, and aminoketone CYP2D6 inhibitor under development for the treatment of Alzheimer's disease (AD) agitation and smoking cessation. AXS-05 utilizes a proprietary formulation and dose of dextromethorphan and bupropion, and Axsome's metabolic inhibition technology, to modulate the delivery of the components. The dextromethorphan component of AXS-05 is an uncompetitive NMDA receptor antagonist, also known as a glutamate receptor modulator, and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan and is a norepinephrine and dopamine reuptake inhibitor. AXS-05 is covered by a robust patent estate extending out to at least 2043. AXS-05 was granted U.S. FDA Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation in June 2020.

About Axsome Therapeutics

Axsome Therapeutics is a biopharmaceutical company leading a new era in the treatment of central nervous system (CNS) conditions. We deliver scientific breakthroughs by identifying critical gaps in care and develop differentiated products with a focus on novel mechanisms of action that enable meaningful advancements in patient outcomes. Our industry-leading neuroscience portfolio includes FDA-approved treatments for major depressive disorder and excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea and multiple late-stage development programs addressing a broad range of serious neurological and psychiatric conditions that impact over 150 million people in the United States. Together, we are on a mission to solve some of the brain's biggest problems so patients and their loved ones can flourish. For more information, please visit the Company's website at www.axsome.com.

Forward Looking Statements

Certain matters discussed in this press release 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 continued commercial success of the Company’s Sunosi® and Auvelity® 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, including statements regarding the ability of the ACCORD and ADVANCE clinical trials to support the filing of an NDA for Alzheimer’s disease agitation; 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; whether issues identified by FDA in the complete response letter may impact the potential approvability of the Company’s NDA for AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to the Company’s special protocol assessment for the MOMENTUM clinical trial; 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 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 continued commercialization of Sunosi and Auvelity 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 press release, and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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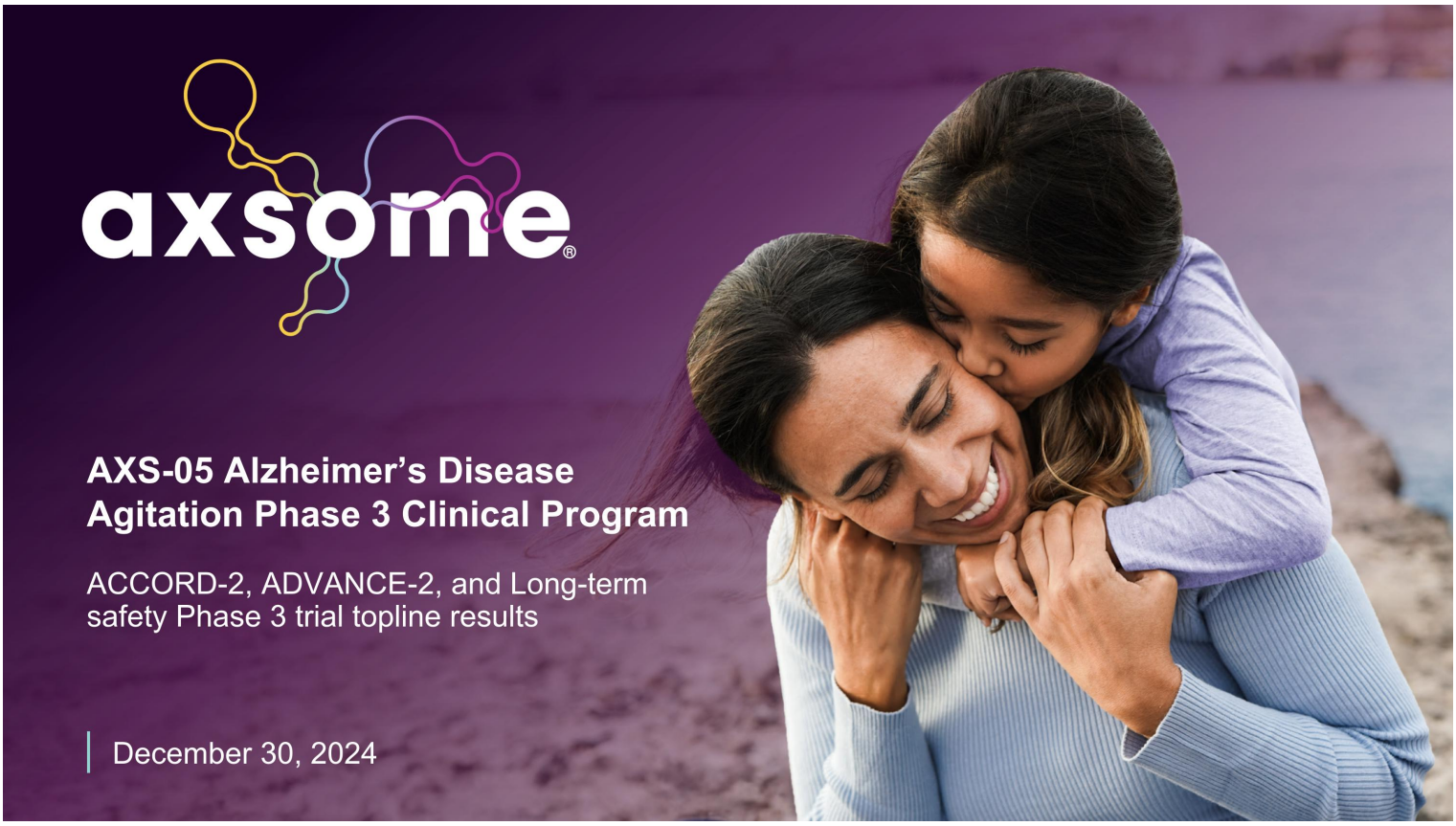
1. Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures.
2. Tractenburg, R.E. et al. Estimating the prevalence of agitation in community-dwelling persons with Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 2002 Winter;14(1):11-8.
3. Porsteinsson, A.P. and Antonsdottir, I.M. An update on the advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother. 2017 Apr;18(6):611-620.


axsome®
AXS-05 Alzheimer's Disease Agitation Phase 3 Clinical Program
ACCORD-2, ADVANCE-2, and Long-term safety Phase 3 trial topline results
December 30, 2024

Forward Looking Statements & Safe Harbor

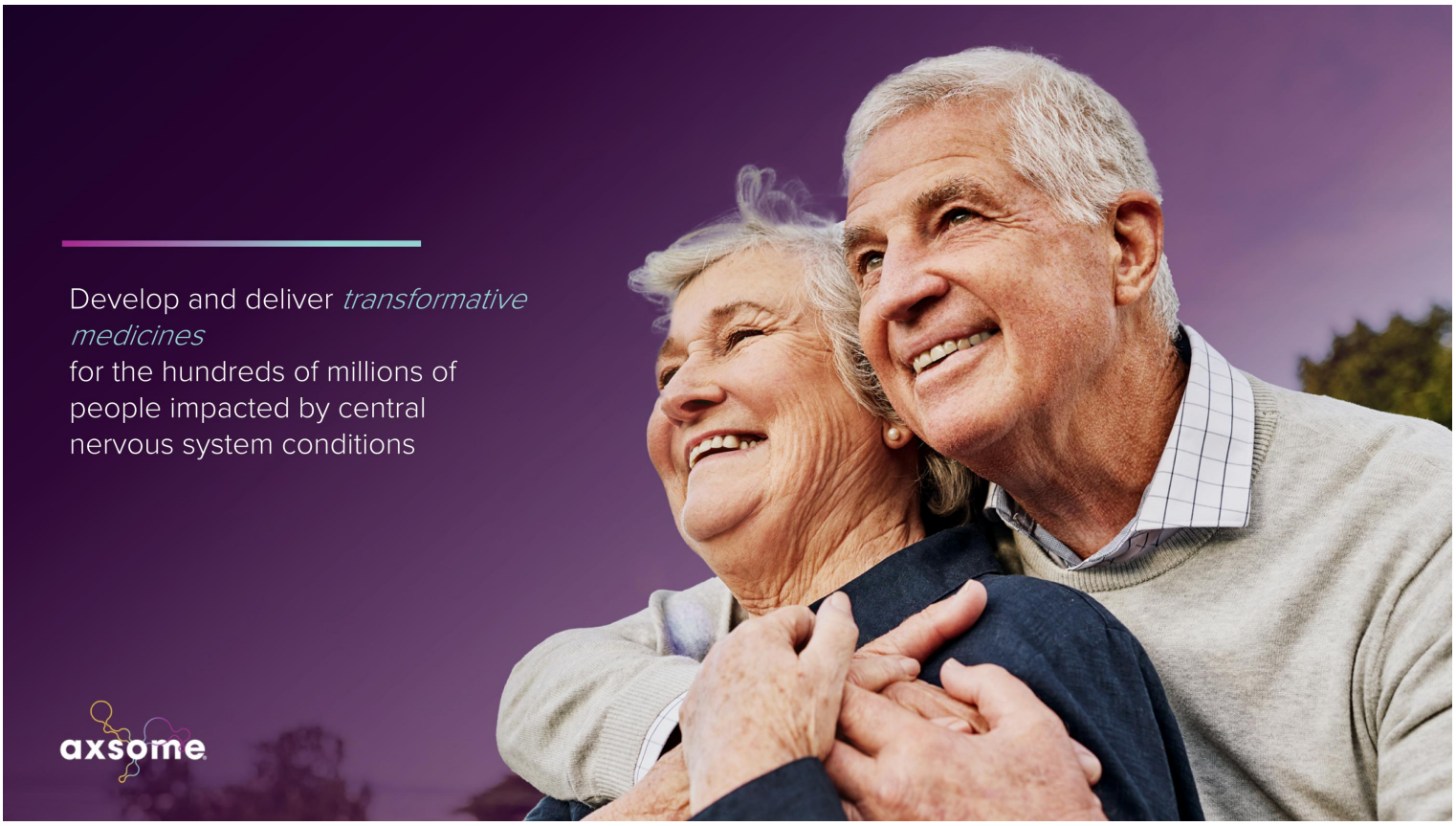
Certain matters discussed in this press release are “forward-looking statements”. The Company may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that 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 continued commercial success of the Company’s Sunosi® and Auvelity® 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, including statements regarding the ability of the ACCORD and ADVANCE clinical trials to support the filing of an NDA for Alzheimer’s disease agitation; 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; whether issues identified by FDA in the complete response letter may impact the potential approvability of the Company’s NDA for AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to the Company’s special protocol assessment for the MOMENTUM clinical trial; 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 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 continued commercialization of Sunosi and Auvelity 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 circumstance.

This presentation contains statements regarding the Company’s observations based upon the reported clinical data. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about the Company's industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, these projections, assumptions and estimates are necessarily subject to a high degree of uncertainty and risk.

Axsome, Auvelity, Sunosi, and MoSEIC, are trademarks or registered trademarks of Axsome Therapeutics, Inc. or its affiliates. Except as with respect to Auvelity and Sunosi for their approved indications, the development products referenced herein have not been approved by the FDA.

Agenda

Introduction	**Mark Jacobson, MA** Chief Operating Officer
Phase 3 trial results ACCORD-2, ADVANCE-2, long-term safety trial	**Herriot Tabuteau, MD** Founder and Chief Executive Officer
Alzheimer's disease agitation Disease overview	**Sue Giordano, PhD** Vice President, Medical Affairs
Clinical perspective	**Dr. Jeffrey Cummings, MD, ScD** Vice Chair of Research, UNLV Department of Brain Health
Q&A	**Dr. Jeffrey Cummings, MD, ScD** **Herriot Tabuteau, MD** **Mark Jacobson, MA** **Sue Giordano, PhD**


Develop and deliver *transformative medicines*
for the hundreds of millions of people impacted by central nervous system conditions
axsome

Summary of topline results

Robust efficacy demonstrated in third pivotal, placebo-controlled trial

- AXS-05 met the primary endpoint in the ACCORD-2 trial by statistically significantly delaying the time to relapse of Alzheimer's disease (AD) agitation compared to placebo (p=0.001)
  - Met key secondary endpoint compared to placebo (p=0.001; prevention of relapse of AD agitation)
  - Reduced worsening of overall AD severity compared to placebo (p<0.001; CGI-S Alzheimer's disease overall clinical status)
- AXS-05 demonstrated numerically greater improvements on primary and secondary endpoints in the ADVANCE-2 trial

Favorable safety and tolerability profile reinforced by long-term, open-label extension trial

- AXS-05 was well tolerated in controlled and long-term trials
- AXS-05 was not associated with death, increased risk of falls, cognitive decline, or sedation
- Long-term safety trial completed with required number of patients treated for 6 and 12 months

AXS-05 (dextromethorphan-bupropion)

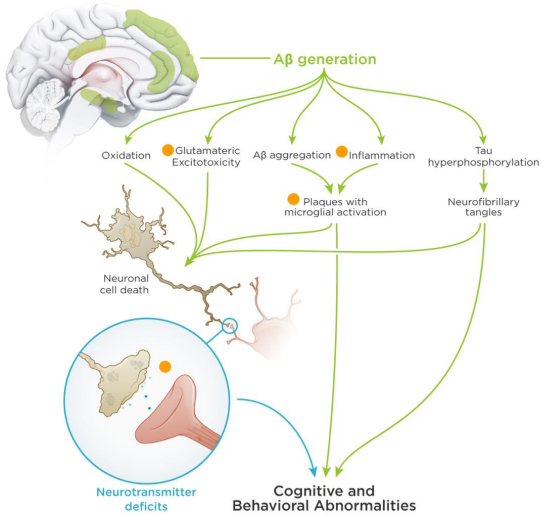
Potentially first-in-class, best-in-class treatment for Alzheimer's disease agitation

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 implicated in Alzheimer's disease (glutamate, sigma-1, norepinephrine, and dopamine)[1-4]

Brain regions implicated in AD agitation[4]



AXS-05 pharmacological actions[5,6]

1. Cummings, J.L. *N Engl J Med.* (2004); 2. Querfurth, H.W. & LaFerla, F.M. *N Engl J Med.* (2010); 3. Porsteinsson, A.P. & Antonsdottir, I.M. *Expert Opin Pharmacother.* (2017); 4. Rosenberg, P.B., Nowrangi, M.A., & Lyketsos, C.G. *Mol Aspects Med.* (2015); 5. Stahl, S.M. *CNS Spectr.* (2019); 6. Cheng, W. et al. *Mol Med Rep.* (2015)

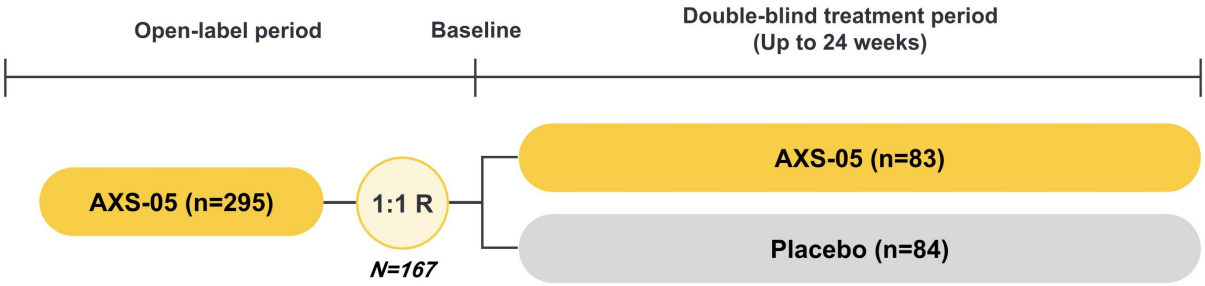
ACCORD-2 Phase 3 trial topline results

ACCORD-1	ADVANCE-1†	ACCORD-2	ADVANCE-2	Long-term safety
Phase 3 (N=108)	*Phase 2/3 (N=366)*	*Phase 3 (N=167)*	*Phase 3 (N=408)*	*Phase 3 (N=456)*
• Efficacy and safety of AXS-05 vs. placebo • 9-week, open-label treatment period followed by 26-week, double-blind, multi-center, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Efficacy and safety of AXS-05 vs. placebo • Open-label treatment period followed by 24-week, double-blind, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Long-term efficacy and safety of AXS-05 • 12-month, open-label extension (OLE) of ACCORD-1 and ADVANCE-2

†Also established component contribution by demonstrating statistical superiority vs. bupropion

ACCORD-2 trial design

Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawal trial



Key eligibility criteria

- 65-90 years of age
- Diagnosis of probable AD (NIA-AA) and clinically significant agitation resulting from probable AD
- MMSE between 10 and 24
- NPI-AA score ≥4

Primary endpoint

- Time from randomization to relapse of agitation

Relapse criteria

- ≥10-point increase (worsening) from randomization in the CMAI total score
- CMAI total score ≥ baseline CMAI total score
- Hospitalization for worsening AD agitation

AD = Alzheimer's disease; NIA-AA = National Institute on Aging-Alzheimer's Association; MMSE = Mini-Mental State Examination; NPI-AA = Neuropsychiatric Inventory-Agitation/Aggression domain

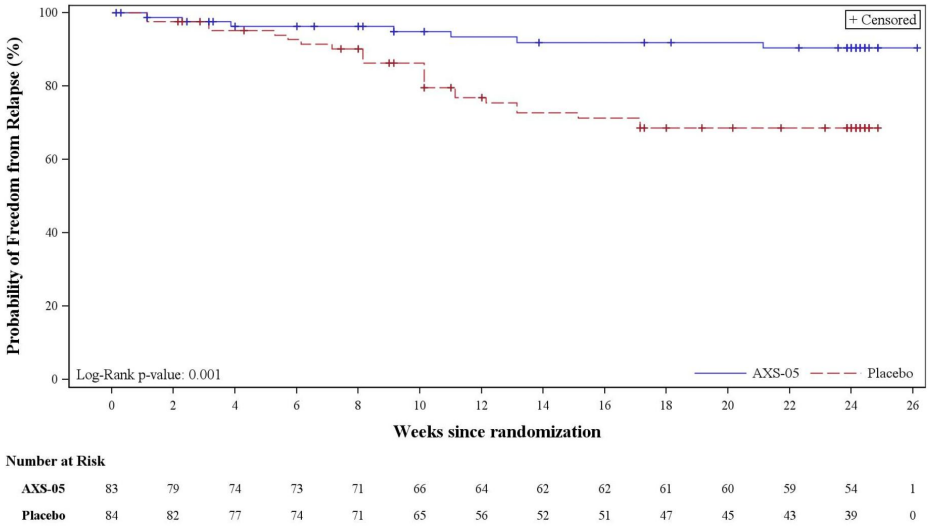
ACCORD-2 demographics and baseline characteristics

	Open-label period	Double-blind period	
	AXS-05 (n=295)	AXS-05 (n=83)	Placebo (n=84)
Age, years (SD)	74.0 (5.3)	73.3 (4.2)	74.2 (5.6)
Female, n (%)	186 (63.1)	54 (65.1)	51 (60.7)
Race, n (%)			
White	268 (90.8)	77 (92.8)	77 (91.7)
Black	26 (8.8)	5 (6.0)	7 (8.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Other or not reported	0 (0.0)	1 (1.2)	1 (0.6)
Baseline CMAI total score	73.3	44.3	45.4
Baseline MMSE score	19.3	21.1	21.7

CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination

Statistically significant delay in the time to relapse of agitation

Primary endpoint (ACCORD-2): Time from randomization to relapse of AD agitation



Number at Risk

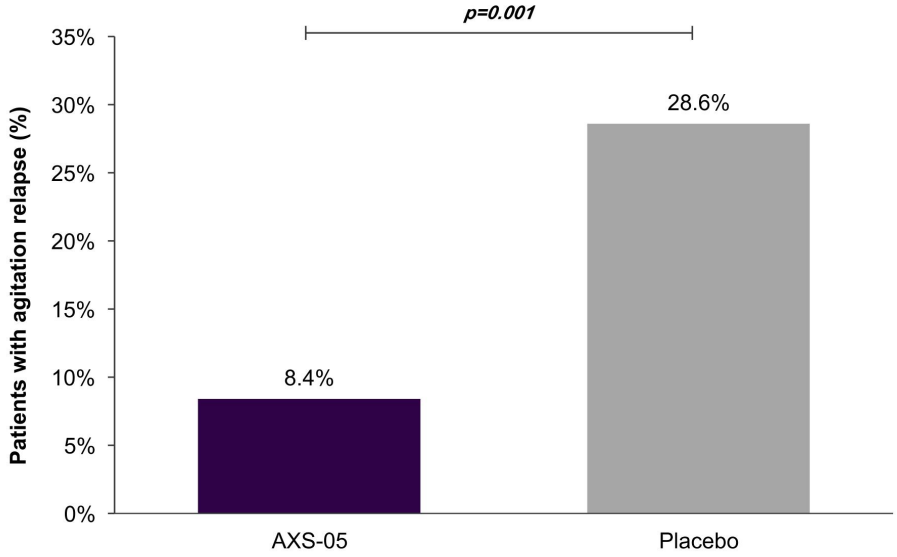
AXS-05	83	79	74	73	71	66	64	62	62	61	60	59	54	1
Placebo	84	82	77	74	71	65	56	52	51	47	45	43	39	0

Hazard Ratio for Time to Relapse	
Hazard Ratio (95% CI)	0.276 (0.119-0.641)
***p*-value**	0.001

AD = Alzheimer's disease

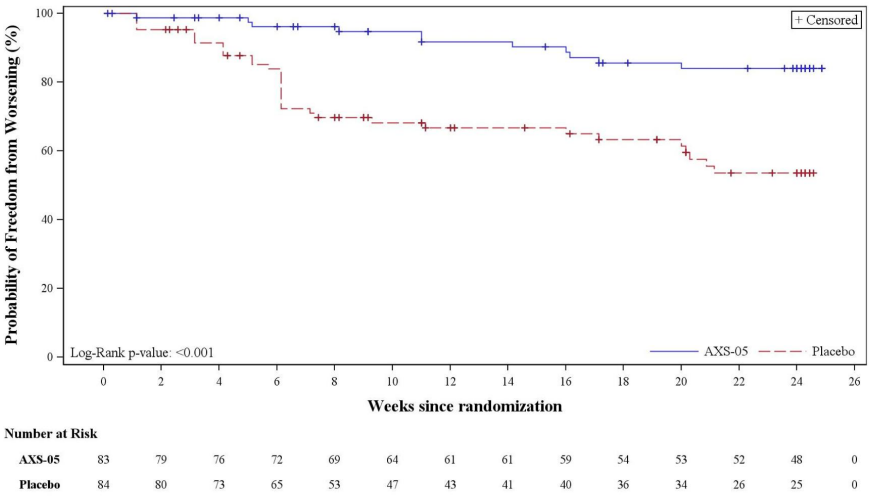
Statistically significant prevention of agitation relapse

Key secondary endpoint (ACCORD-2): Prevention of relapse of Alzheimer's disease agitation



Reduced worsening of overall Alzheimer's disease severity

ACCORD-2



Number at Risk

AXS-05	83	79	76	72	69	64	61	61	59	54	53	52	48	0
Placebo	84	80	73	65	53	47	43	41	40	36	34	26	25	0

Percent of patients with worsening AD severity (CGI-S Alzheimer's disease overall clinical status)		
AXS-05	**Placebo**	***p*-value**
13.3%	39.3%	<0.001

ACCORD-2 summary of adverse events

	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)
Back pain	3 (3.7)	0 (0.0)

- Falls reported in 2 patients (2.4%) in the AXS-05 group; only one deemed related to study medication
- No deaths reported in either treatment group
- AXS-05 was not associated with deaths, sedation, or cognitive decline as measured by the MMSE

TEAE = treatment emergent adverse event

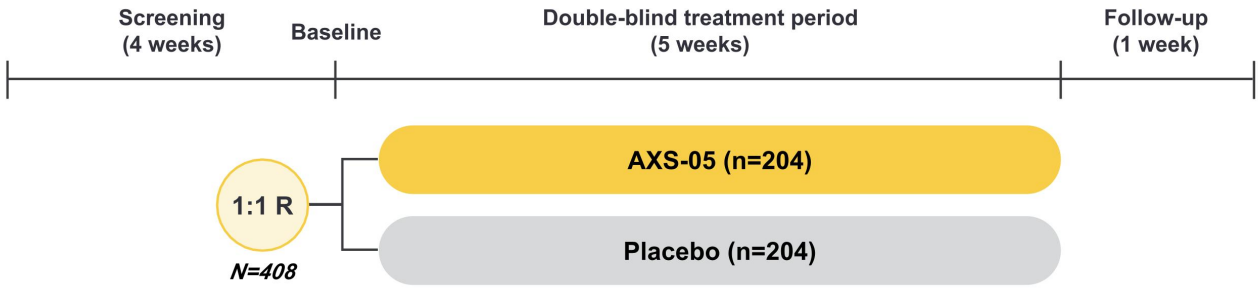
ADVANCE-2 Phase 3 trial topline results

ACCORD-1	ADVANCE-1†	ACCORD-2	ADVANCE-2	Long-term safety
Phase 3 (N=108)	*Phase 2/3 (N=366)*	*Phase 3 (N=167)*	*Phase 3 (N=408)*	*Phase 3 (N=456)*
• Efficacy and safety of AXS-05 vs. placebo • 9-week, open-label treatment period followed by 26-week, double-blind, multi-center, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Efficacy and safety of AXS-05 vs. placebo • Open-label treatment period followed by 24-week, double-blind, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Long-term efficacy and safety of AXS-05 • 12-month, open-label extension (OLE) of ACCORD-1 and ADVANCE-2

†Also established component contribution by demonstrating statistical superiority vs. bupropion

ADVANCE-2 trial design

Phase 3, multi-center, randomized, double-blind, placebo-controlled trial



Key eligibility criteria

- 65-90 years of age
- Diagnosis of probable AD (NIA-AA) and clinically significant agitation resulting from probable AD
- MMSE between 10 and 24
- NPI-AA score ≥4

Dose titration

- AXS-05 30 mg/105 mg once daily escalated up to 45 mg/105 mg twice daily

Primary endpoint

- Change from baseline in CMAI total score compared to placebo at Week 5

AD = Alzheimer's disease; NIA-AA = National Institute on Aging-Alzheimer's Association; MMSE = Mini-Mental State Examination; NPI-AA = Neuropsychiatric Inventory-Agitation/Aggression domain; CMAI = Cohen-Mansfield Agitation Inventory

ADVANCE-2 demographics and baseline characteristics

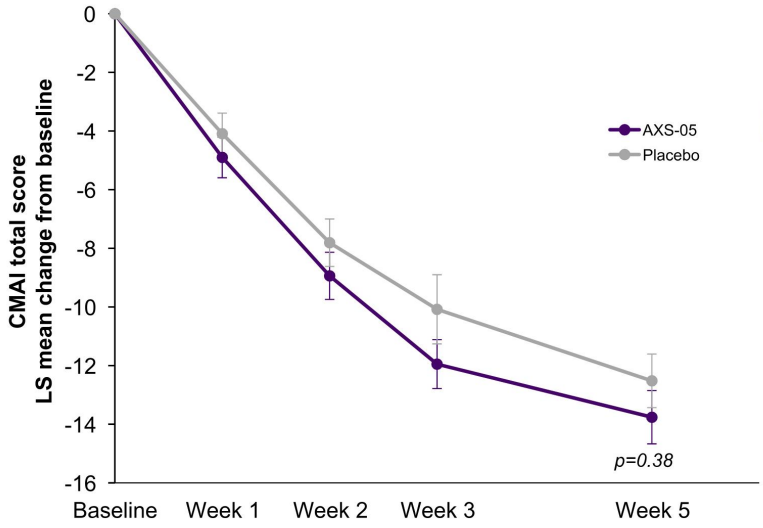
ITT population

	AXS-05 (n=204)	Placebo (n=204)
Age, years (SD)	73.6 (5.3)	75.0 (5.7)
Female, n (%)	130 (63.7)	112 (54.9)
Race, n (%)		
White	184 (90.2)	178 (87.3)
Black	18 (8.8)	23 (11.3)
Asian	2 (1.0)	2 (1.0)
Other or not reported	0 (0.0)	1 (0.5)
Baseline CMAI total score	71.0	73.5
Baseline MMSE score	19.2	19.1

CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination

Improvement in symptoms of agitation

Primary endpoint (ADVANCE-2): Change from baseline in CMAI total score at Week 5



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

CMAI = Cohen-Mansfield Agitation Inventory

ADVANCE-2 summary of adverse events

Safety population

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)
Most common TEAEs (≥3% in AXS-05 group)		
Dizziness	12 (5.9)	3 (1.5)
Headache	9 (4.4)	7 (3.4)

- Falls reported in one patient (0.5%) in each treatment arm, which was deemed unrelated to study medication in the AXS-05 group
- No deaths reported in either treatment group
- AXS-05 was not associated with death, sedation, or cognitive decline as measured by the MMSE

TEAE = treatment emergent adverse event

Long-term safety trial topline results

ACCORD-1	ADVANCE-1†	ACCORD-2	ADVANCE-2	Long-term safety
Phase 3 (N=108)	*Phase 2/3 (N=366)*	*Phase 3 (N=167)*	*Phase 3 (N=408)*	*Phase 3 (N=456)*
• Efficacy and safety of AXS-05 vs. placebo • 9-week, open-label treatment period followed by 26-week, double-blind, multi-center, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Efficacy and safety of AXS-05 vs. placebo • Open-label treatment period followed by 24-week, double-blind, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Long-term efficacy and safety of AXS-05 • 12-month, open-label extension (OLE) of ACCORD-1 and ADVANCE-2

†Also established component contribution by demonstrating statistical superiority vs. bupropion

Long-term safety trial summary of adverse events

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)

- Falls reported in 3.1% of patients, with only 0.2% deemed related to study medication
- No deaths occurred in the trial
- None of the serious TEAEs were deemed related to study drug
- AXS-05 was not associated with death, sedation, or cognitive decline as measured by the MMSE

TEAE = treatment emergent adverse event

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

ADVANCE-1	ADVANCE-2	ACCORD-1	ACCORD-2
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
N=366	*N=408*	*N=108*	*N=167*
Primary endpoint: Mean reduction from baseline in CMAI total score at Week 5 of 15.4 points for AXS-05 and 11.5 points for placebo (p=0.010)	Primary endpoint: Mean reduction from baseline in CMAI total score at Week 5 of 13.8 points for AXS-05 and 12.6 points for placebo (p=0.380)	Primary endpoint: Time to relapse: hazard ratio of 0.275 (p=0.014)	Primary endpoint: Time to relapse: hazard ratio of 0.276 (p=0.001)

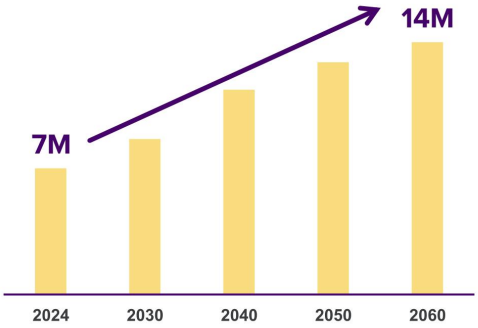
Alzheimer’s disease agitation

Sue Giordano, PhD

Vice President of Medical Affairs

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 approximately ***7M*** people in the U.S.[1]

Agitation is reported in ***~70%*** of people with AD and is characterized by emotional distress, verbal and physical aggressiveness, disruptive irritability, and disinhibition[1,2]

Psychosocial interventions of AD agitation, while recommended as first line treatment, are not always effective[3]

1. Alzheimer’s Association (2024); 2. Trachtenberg et al. *J Neuropsychiatry Clin Neurosci.* (2002); 3. Porsteinsson, A.P. & Antonsdottir, I.M. *Expert Opin Pharmacother.* (2017)

The four IPA criteria for agitation in cognitive disorders[1]

Cognitive impairment or dementia syndrome

- Patient meets criteria for a cognitive impairment or dementia syndrome, including:
  - Alzheimer's disease
  - Mild cognitive impairment
  - Other dementias

Agitation behavior and duration

- ≥1 agitation behavior associated with emotional distress
- Behavior is persistent, frequently recurring for ≥2 weeks, or represents a change form the patient's usual behavior

Agitation behavior severity

- Behavior(s) is severe and associated with excess distress or produces excess disability beyond that due to cognitive impairment
- Significantly impairs ≥1 of the following:
  - Interpersonal relationships
  - Other aspects of social functioning
  - Ability to perform or participate in daily activities

Cause of agitation behavior

- Agitation is not attributable to:
  - Another psychiatric disorder or medical condition
  - Suboptimal care conditions
  - Physiological effects of a substance

1. Cummings, J., et al. *Int Psychogeriatr.* (2015)
IPA = International Psychogeriatric Association

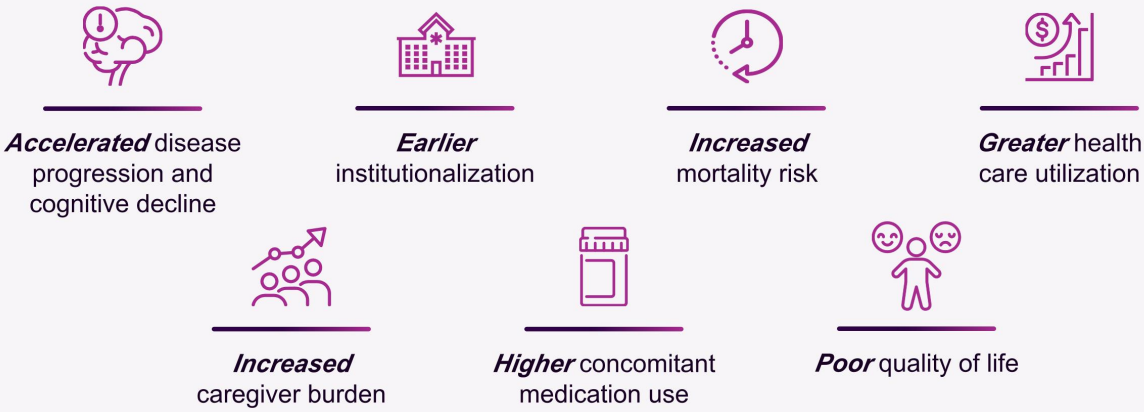
Agitation is a common behavioral symptom that may present in ~70% of patients with Alzheimer's disease[1,2]

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

1. Alzheimer's Association (2024); 2. Tractenberg, R.E. et al. *J Neuropsychiatry Clin Neurosci.* (2002); 3. Cummings, J., et al. *Int Psychogeriatr.* (2015); Sano, M., et al. *Int Psychogeriatr.* (2023)

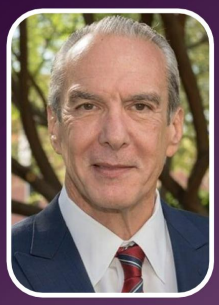
Agitation worsens impact of Alzheimer's disease and adds significant burden on patient and caregiver

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



1. Porsteinsson, A.P. & Antonsdottir, I.M. *Expert Opin Pharmacother.* (2017); 2. Fillit, H., et al. *Int J Geriatr Psychiatry* (2021); 3. Jones, E., et al. *J Alzheimers Dis.* (2021)

Clinical perspective



Dr. Jeffrey Cummings, MD, ScD

Vice Chair of Research, UNLV Department of Brain Health

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.
- Current pharmacologic treatments are primarily off-label medications:
  - Typical and atypical antipsychotics, benzodiazepines, antiepileptics, antidepressants
- Limitations of off-label medications:
  - Sedation, extrapyramidal side effects, falls, worsening of cognition, cardiovascular and cerebrovascular events
  - 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

Challenges for clinical trials of agents for the treatment of neuropsychiatric syndromes

Multiple specific challenges

- Robust placebo-group improvement:
  - True placebo response
  - Caregiver placebo response
  - Trial and clinician response
- Issues with scales and raters
- Disease complexity and natural history of agitation

Benefits of randomized withdrawal trials

- Mitigates against placebo response:
  - All subjects treated with active therapy
  - Responders randomly assigned to active or placebo
- Assesses rate or time to symptom response, maintenance of effect
- Type 1 error control in conjunction with parallel group trial

1. Zhu, 2021. Front. Psychiatry 11:562660. 2. Dowden and Munro J. Nat Rev Drug Discov. 2019 Jul;18(7):495-496. 3. Wong, Siah, and Lo. Biostatistics. 2019 Apr 1;20(2):273-286. 4. Hopkins et al. Current Medical Research and Opinion, 39:3, 467-471

Perspective on AXS-05 in Alzheimer's disease agitation

Comprehensive Phase 3 clinical program

- Four controlled Phase 3 clinical trials evaluated AXS-05 in Alzheimer's disease agitation
- Two distinct trial paradigms (parallel group and randomized withdrawal) is a strength
- Program evaluated both induction and maintenance effects of therapy

Efficacy of AXS-05 in Alzheimer's disease agitation

- Strong statistically significant and clinically meaningful efficacy demonstrated in ADVANCE-1, ACCORD-1, and ACCORD-2
- Global improvement in Alzheimer's disease severity observed

Safety of AXS-05 in Alzheimer's disease agitation

- Well tolerated across controlled and long-term studies
- ADVANCE-2 provides supportive controlled safety data
- No association with death, increased risk of falls, sedation, or cognitive decline observed

Q&A