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Efficacy and Safety of AXS-05 in Alzheimer's Disease Agitation: Results From ACCORD-1, a Phase-3, Double-Blind, Placebo-Controlled, Relapse Prevention Study

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Key Objective

To evaluate the efficacy and safety of AXS-05 in patients with Alzheimer's disease (AD) agitation

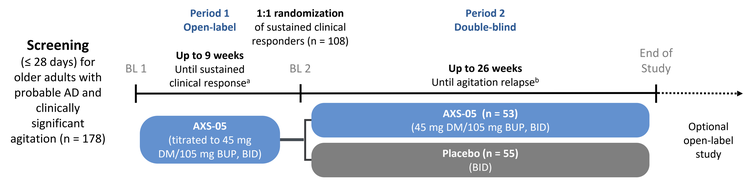
Introduction

- AD agitation is reported in up to 70% of people with AD and is characterized by emotional distress, aggressive behavior, disruptive irritability, and disinhibition[1,2]
- AD agitation is associated with increased caregiver burden, reduced functioning, faster cognitive decline, earlier transition to long-term care, and increased mortality[3,4,5]
- Non-pharmacological therapies for AD agitation, while recommended as first-line therapy, are not always effective[3,5]
- Pharmacotherapies for AD agitation exhibit limited efficacy and carry considerable safety concerns, leaving an unmet need for novel and effective pharmacological treatments with favorable safety and tolerability profiles[6]
- AXS-05 (dextromethorphan-bupropion) is a novel, oral N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and aminoketone CYP2D6 inhibitor approved by the US FDA for the treatment of major depressive disorder in adults[7]

Methods

Figure 1: ACCORD-1 randomized discontinuation study design

- The ACCORD-1 study (Assessing Clinical Outcomes in Alzheimer's Disease Agitation; NCT04797715) was a Phase 3, double-blind, placebo-controlled, randomized withdrawal study to evaluate the efficacy and safety of AXS-05 in the treatment of AD agitation



Primary Endpoint: Time from randomization to relapse of agitation

Key Secondary Endpoint: Percentage of participants who relapsed

[a]Sustained response of ≥ 30% improvement from baseline in the CMAI total score and improvement on the PGI-C (score ≤ 3) that were both maintained for ≥ 4 consecutive weeks.
[b]Agitation relapse defined as a ≥ 10-point worsening in the CMAI total score from randomization or a CMAI total score greater than that at study entry; or hospitalization or other institutionalization due to AD agitation.
AD, Alzheimer's disease; AD agitation, Alzheimer's disease agitation; BID, twice daily; BL, baseline; BUP, bupropion; CMAI, Cohen-Mansfield Agitation Inventory; DM, dextromethorphan; PGI-C, Patient Global Impression of Change

Table 1. ACCORD-1 Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
• Age 65-90 years (inclusive) • Probable AD according to 2011 NIA-AA criteria[7] • Agitation according to IPA provisional definition[8] • MMSE score 10-24 (inclusive)[a] • NPI-AA score ≥ 4 • Caregiver participation	• Predominantly non-AD dementia • Agitation symptoms not secondary to AD • Concurrent medical condition that may interfere with study conduct • Medically inappropriate in opinion of investigation

[a]An MMSE score ≤ 24 is generally used as indicative of cognitive impairment
AD, Alzheimer's disease; IPA, International Psychogeriatric Association; MMSE, Mini-Mental State Examination; NIA-AA National Institute on Aging - Alzheimer's Association; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor.

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Acknowledgments

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QR Code

Scan the code at the top of this poster or access **https://www.axsomecongresshub.com/AGS2025.shtml** to view or download a PDF or access additional information.

Disclosures

J. Cummings has provided consultation to Acadia, Acumen, ALZpath, Annovis, Aprinoia, Artery, Axsome Therapeutics, Biogen, Biohaven, BioXcel, Bristol-Myers Squib, Eisai, Fosun, GAP Foundation, Green Valley, Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, sinaptica, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. He is supported by US National Institute of General Medical Sciences (NIGMS) grant P20GM109025, National Institute on Aging (NIA) grant R35AG71476, NIA grant R25 AG083721-01, the Alzheimer's Disease Drug Discovery Foundation (ADDF), the Ted and Maria Quirk Endowment, and the Joy Chambers-Grundy Endowment.

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C. Streicher, C. Zeni, and **H. Tabuteau** are current employees of Axsome Therapeutics.

Results

Patient Population

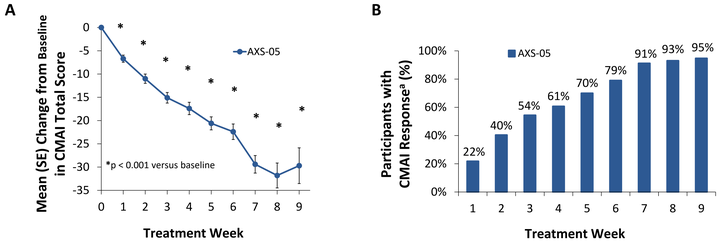
Table 2. Demographics and Baseline Characteristics

	Open-Label Period	Double-Bind Period	
	AXS-05 (n = 178)	AXS-05 (n = 53)	Placebo (n = 55)
Age, years, mean (SD)	74.9 (6.0)	74.1 (6.0)	74.9 (6.2)
Female Gender, n (%)	95 (53.4)	27 (50.9)	30 (54.5)
Race, n (%)			
White	152 (85.4)	45 (84.9)	47 (85.5)
Black or African American	18 (10.1)	4 (7.5)	7 (12.7)
Asian	4 (2.2)	2 (3.8)	1 (1.8)
Other	4 (2.2)	2 (3.8)	0
CMAI total score, mean (SD)	70.9 (22.3)	43.7 (10.2)	44.9 (10.9)
NPI-AA total score, mean (SD)[a]	7.0 (2.0)	4.1 (2.0)	3.6 (1.9)
CGI-S agitation, mean (SD)	4.3 (0.6)	2.7 (0.8)	2.9 (0.8)
MMSE total score, mean (SD)	17.8 (4.0)	17.8 (4.8)	18.5 (4.4)

[a]NPI-AA total score n = 49 participants in both AXS-05 and placebo groups in the double-blind period.
CGI-S, Clinical Global Impression –Severity; CMAI, Cohen-Mansfield Agitation Inventory; ITT, intent-to-treat; MMSE, Mini Mental state examination; NPI-AA, Neuropsychiatric Inventory – Agitation and Aggression domain.

ACCORD-1 Efficacy

Figure 2. Open-Label Period CMAI Mean Change From Baseline (A) and Clinical Response (≥ 30% Reduction) on CMAI (B)

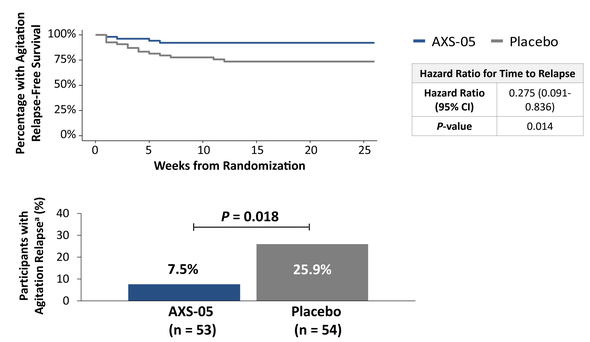


[a]CMAI response defined as ≥ 30% reduction from baseline.
CMAI, Cohen-Mansfield Agitation Inventory.

- Statistically significant improvement from baseline on the CMAI was seen with open-label AXS-05 treatment at all timepoints starting at Week 1 ($P < 0.001$); **Figure 2A**)
- Clinical response (≥ 30% CMAI reduction) was observed in nearly 80% of participants by Week 6; **Figure 2B**)

ACCORD-1 Efficacy

Figure 3. Double-Blind Period Kaplan-Meier Plot of Time from Randomization to Relapse of Agitation Symptoms (A) and relapse prevention (B)



[a]Agitation relapse defined as a ≥ 10-point worsening (increase) in the CMAI total score from randomization or a CMAI total score greater than that at study entry for 2 consecutive weeks.
CMAI, Cohen-Mansfield Agitation Inventory; mITT, modified intent-to-treat.

- AXS-05 substantially and statistically increased the time to relapse of agitation symptoms compared with placebo (Hazard ratio, 0.275; P=0.014; **Figure 3A**); risk of relapse was 3.6-fold lower with AXS-05 compared with placebo
- Significantly fewer patients treated with AXS-05 relapsed compared to placebo treated patients (7.5% vs 25.9% of participants; P=0.018; **Fig 3B**)

Safety

Table 3. Summary of Treatment-Emergent Adverse Events

	Double-Blind Period[a]	
n (%)	AXS-05 (n = 53)	Placebo (n = 55)
Participant with ≥ 1 TEAE[b]	15 (28.3)	12 (22.2)
Serious TEAE	1 (1.9)	2 (3.7)
Participant with TEAE leading to study discontinuation	0	1 (1.9)
Participant with TEAE leading to death	0	1 (1.9)[c]

[a]Safety Population includes all subjects who receive at least 1 dose of AXS-05. [b]During the ACCORD-1 double-blind period, there were 3 (5.7%) and 2 (3.7) patients with drug-related TEAEs in the AXS-05 and Placebo arm, respectively. [c]Death due to cardiac arrest.
MMSE, Mini Mental State Examination; TEAE, treatment-emergent adverse event.

- The most frequently reported TEAEs in ≥ 5% of patients in any arm (AXS-05 and placebo, respectively) were diarrhea (7.5% and 3.7%), fall (7.5% and 3.7%), and back pain (5.7% and 3.7%)
- Falls were reported in 4 participants in the AXS-05 group, none of which were related to study medication or associated with serious AEs, and in 2 participants in the placebo group, one of which was associated with a femur fracture

Conclusions

- AXS-05 significantly increased the time to relapse of agitation symptoms compared with placebo in the double-blind period
- Improvement of agitation symptoms with AXS-05 was rapid and durable in the initial open-label period
- Overall, AXS-05 was generally well tolerated with no new safety signals identified from the prior phase 2 trial
- No sedation treatment-emergent adverse events, clinically significant cardiovascular changes, or evidence of cognitive decline were observed in participants treated with AXS-05 in this study
- AXS-05 is a promising candidate for the treatment of agitation in patients with Alzheimer's disease