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Efficacy and Safety of AXS-05 in Alzheimer's Disease Agitation: Results From ACCORD-2, a Phase 3 Randomized Withdrawal Double-Blind Placebo-Controlled Study

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Key Objective

To report results from ACCORD-2, a Phase-3, multicenter, double-blind, placebo-controlled, randomized withdrawal study of AXS-05 in Alzheimer's disease agitation

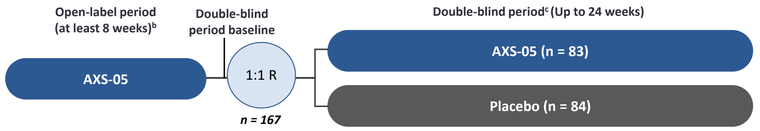
Introduction

- Alzheimer's disease (AD) agitation is a neuropsychiatric symptom that affects approximately 70% of patients with AD and presents as emotional distress, aggressive behavior, disruptive irritability, and disinhibition[1,2]
- These symptoms are associated with greater caregiver burden, reduced functioning, faster cognitive decline, earlier transition to long-term care, and increased mortality[3,4]
- Non-pharmacologic, psychosocial interventions are recommended as first-line treatment, but are not always effective[5]
- Pharmacotherapies for AD agitation are often used off-label, 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 Food and Drug Administration for the treatment of major depressive disorder in adults[7]
  - Efficacy and safety of AXS-05 for the treatment of AD agitation was demonstrated in the ADVANCE-1 and ACCORD-1 Phase 2/3 studies[8,9]

Methods

ACCORD-2 Trial Design

- ACCORD-2 (NCT04947553) was a Phase-3, multicenter, double-blind, placebo-controlled, randomized withdrawal study of AXS-05 in AD agitation
- To show maintenance of effect, participants achieving a sustained clinical response[a] and completing ≥ 8 weeks of open-label treatment were eligible to enter the double-blind segment



Primary Endpoint: Time to relapse of AD agitation vs placebo

Key Secondary Endpoint: Rates of relapse in AXS-05 vs placebo participants

Table 1. Key Inclusion and Exclusion Criteria

Inclusion	Exclusion
• 65-90 years of age • Probable AD (NIA-AA) and diagnosis of agitation according to the IPA provisional definition of agitation • MMSE between 10 and 24 • NPI-AA score ≥4 • Completion of the treatment period in ADVANCE-2	• Predominantly non-AD dementia • Agitation symptoms not secondary to AD • Concurrent medical condition that may interfere with study conduct

AD , Alzheimer's disease; CMAI, Cohen-Mansfield Agitation Inventory; IPA, International Psychogeriatric Association; MMSE, Mini-Mental State Examination; NIA-AA, National Institute on Aging-Alzheimer's Association; NPI-AA, Neuropsychiatric Inventory-Agitation/Aggression domain; R, randomization. [a]Sustained clinical response is defined as ≥ 5 point improvement from the Baseline visit in the ADVANCE-2 study (from which patients in ACCORD-2 were carried over) in the CMAI total score and improvement on the PGI-C (score of ≤ 3) that are both maintained over a period of at least 4 consecutive weeks starting at Week 4. [b]Eligible participants from the ADVANCE-2 were carried over to participate in ACCORD-2. [c]Participants who completed the double-blind treatment or had a relapse were eligible to return to OL treatment, if their total participation did not exceed 52 weeks.

Results

Participant Population

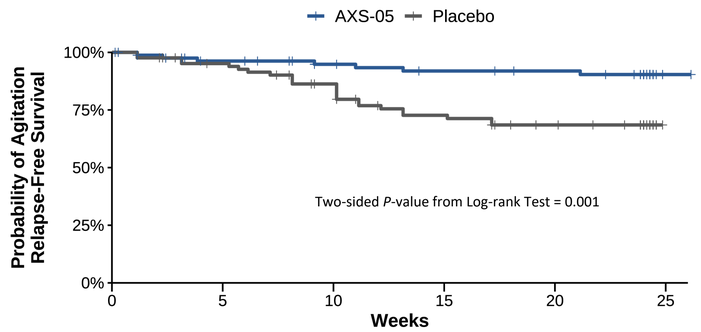
Table 2: Demographics and Baseline Characteristics

	Open-label period	Double-blind period	
	AXS-05 (N = 295)	AXS-05 (n = 83)	Placebo (n = 84)
Mean 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
Other or not reported	1 (0.3)	1 (1.2)	0
Mean baseline CMAI total score[a]	73.3	44.3	45.4
Mean baseline MMSE score[a]	19.3	21.1	21.7

CMAI, Cohen-Mansfield Agitation Inventory; MMSE, Mini-Mental State Examination.
[a]Baseline characteristics in the Open-label period column of this table represent baseline values from the ADVANCE-2 trial from which participants in the ACCORD-2 trial were carried over.

Time to Relapse (Primary Endpoint)

Figure 1. Kaplan-Meier Plot of Time from Randomization to Relapse of Agitation Symptoms



Agitation relapse defined as:
- ≥10-point increase (worsening) from randomization in the CMAI total score for 2 consecutive weeks *or* CMAI total score at assessment ≥ baseline[a] CMAI total score for 2 consecutive weeks
- Hospitalization for worsening AD agitation

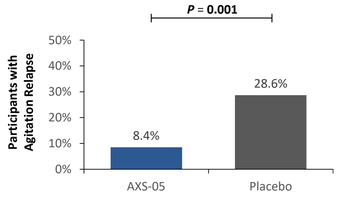
- ACCORD-2 met its primary endpoint by significantly delaying the time to relapse of AD agitation with AXS-05 versus placebo (hazard ratio, 0.276)
- Risk of relapse was 3.6-fold less with AXS-05 compared to placebo

Hazard Ratio for Time to Relapse	
Hazard Ratio (95% CI)	0.276 (0.119-0.641)

[a]Baseline values are from the ADVANCE-2 trial from which participants in the ACCORD-2 trial were carried over.
AD, Alzheimer's disease; CMAI, Cohen-Mansfield Agitation Inventory.

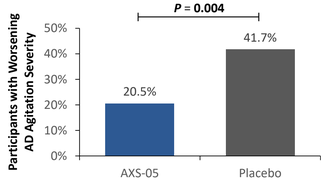
Relapse Prevention and Worsening of AD Agitation

Figure 2. Relapse Prevention of AD Agitation



- AXS-05 met the key secondary endpoint by significantly preventing relapse of AD agitation compared to placebo (8.4% vs 28.6%; P = 0.001)

Figure 3. Prevention of Worsening of AD Agitation



- AXS-05 significantly reduced worsening of AD agitation compared to placebo as assessed by CGI-S agitation (20.5% vs 41.7%; P = 0.004)

AD, Alzheimer's disease; CGI-S, Clinical Global Impression-Severity.

Safety

Table 3. Summary of Treatment-Emergent Adverse Events

n (%)	Double-blind period	
	AXS-05 (n = 82)	Placebo (n = 84)
Incidence of TEAEs	24 (29.3)	27 (32.1)
Incidence of serious TEAEs	0	2 (2.4)
Discontinuation due to TEAEs	0	1 (1.2)
TEAEs in ≥ 3% of the 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

- AXS-05 was well tolerated, with no new safety signals
- Falls were reported in 2 participants (2.4%) in the AXS-05 group; only one deemed related to study medication
- Dizziness was reported in 1 participant in the AXS-05 group
- AXS-05 was not associated with sedation or cognitive decline as measured by MMSE
- No deaths were reported in either treatment group

MMSE, Mini Mental State Examination; TEAE, treatment-emergent adverse event.

Conclusions

- The ACCORD-2 Phase 3 trial achieved the primary endpoint, with AXS-05 statistically significantly delaying the time to relapse of AD agitation compared to placebo
- ACCORD-2 also met the key secondary endpoint (prevention of relapse of AD agitation), and reduced worsening for AD agitation compared to placebo, as assessed by CGI-S for AD agitation
- AXS-05 was well tolerated, with no new safety signals
- These results support the use of AXS-05 as a safe and effective treatment for AD agitation, building on data from previous positive Phase 2/3 studies
- If approved, AXS-05 would be a new treatment with a novel mechanism of action for the treatment of AD agitation

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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. G. Grossberg has provided consultation to Acadia, Alkahest, Avanir, Axovant, Axsome Therapeutics, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Otsuka, Roche, and Takeda. He has provided research support for Lilly, Roche, and the National Institute on Aging. He has served on a Speaker's Bureau for Acadia, Biogen, and Eisai and has served on Safety Monitoring Committees for Anavex, EryDel, IntracellularTherapies, Merck, Newron, and Oligomerix. C. Streicher, B. Pfister and H. Tabuteau are current employees of Axsome Therapeutics.