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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

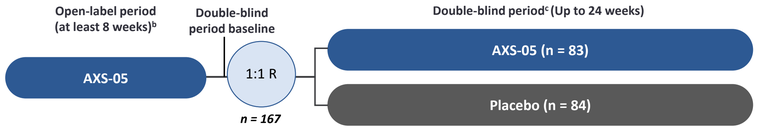
Introduction

- 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

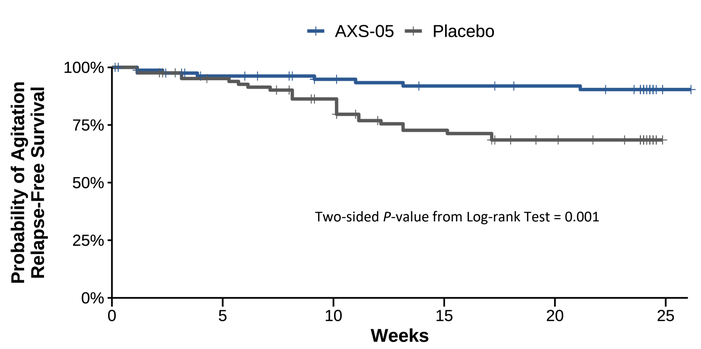
Table 2: Demographics and Baseline Characteristics

	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

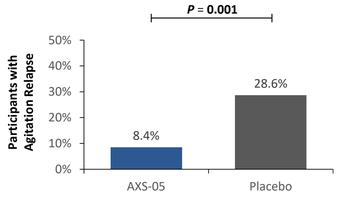
- ACCORD-2 met its primary endpoint by significantly delaying the time to relapse of AD agitation with AXS-05 versus placebo (hazard ratio, 0.276)
- Risk of relapse was 3.6-fold less with AXS-05 compared to placebo

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.

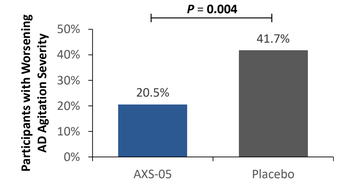
Relapse Prevention and Worsening of AD Agitation

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
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