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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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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, Julius Clinical, 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 and **H. Tabuteau** are current employees of Axsome Therapeutics.

Introduction

- Alzheimer's disease (AD) agitation affects up to 70% of patients with AD[1]
- Pharmacotherapies 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 tolerability[2]
- 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 (FDA) for the treatment of major depressive disorder in adults[3]
- AXS-05 is being investigated for the treatment of AD agitation and has been granted Breakthrough Therapy Designation by the FDA[4]
- 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[5,6]

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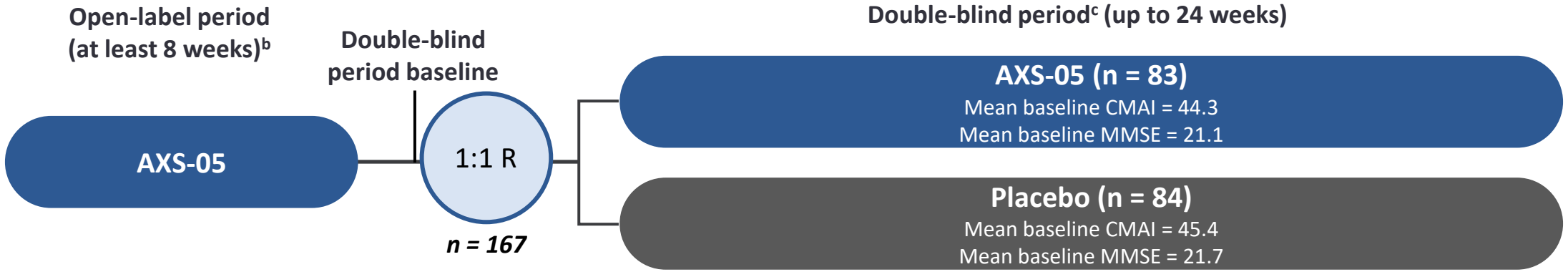
Study Design

- ACCORD-2 (NCT04947553) was a Phase 3, multicenter, double-blind, placebo-controlled randomized withdrawal study of AXS-05 in Alzheimer's Disease (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



Key Inclusion Criteria: Participants 65-90 years of age with clinical diagnosis of probable AD (based on NIA-AA), and a clinical diagnosis of agitation (based on IPA provisional definition of agitation)

Primary Endpoint: Time to relapse of AD agitation versus placebo

Key Secondary Endpoint: Rate of relapse in AXS-05 versus placebo participants

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; 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.

Participant Population

- Sociodemographic and baseline characteristics were generally similar between treatment groups

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

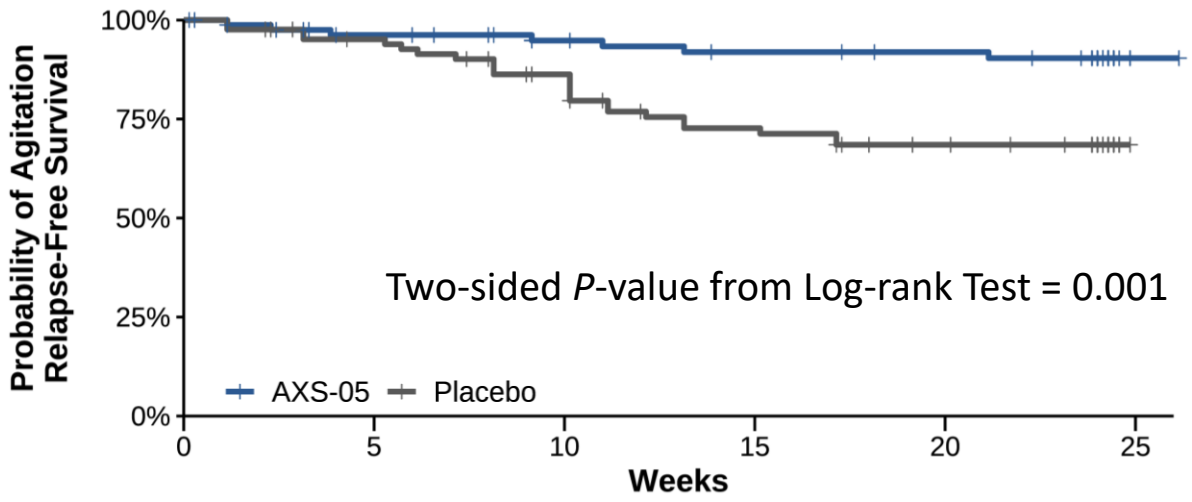
CMAI, Cohen-Mansfield Agitation Inventory; MMSE, Mini-Mental State Examination.

[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.

Efficacy: Key Primary Endpoint – Time to Relapse

- 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

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

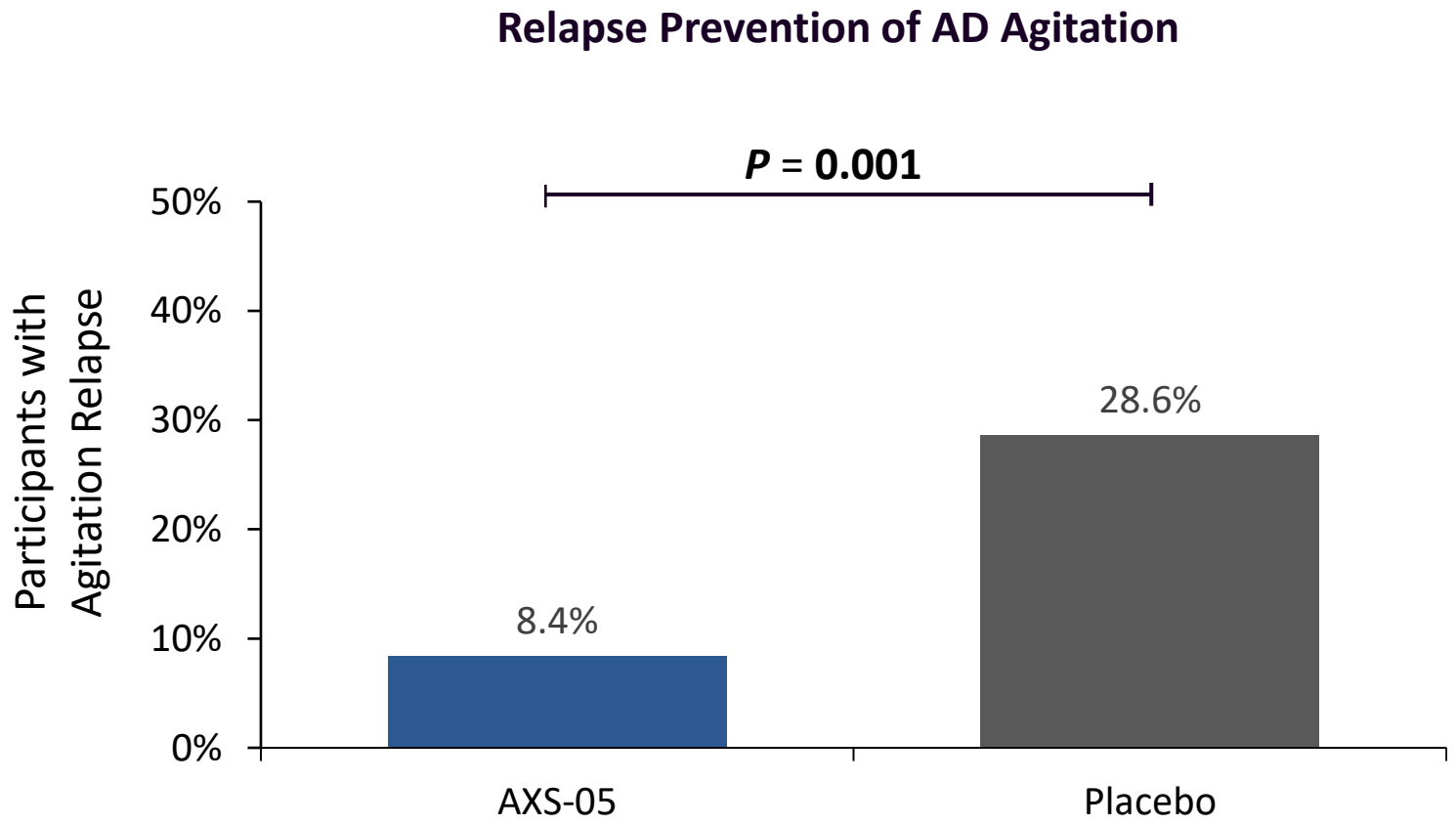
Hazard Ratio for Time to Relapse	
Hazard Ratio (95% CI)	0.276 (0.119-0.641)

[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.

Efficacy: Key Secondary Endpoint – Relapse Prevention

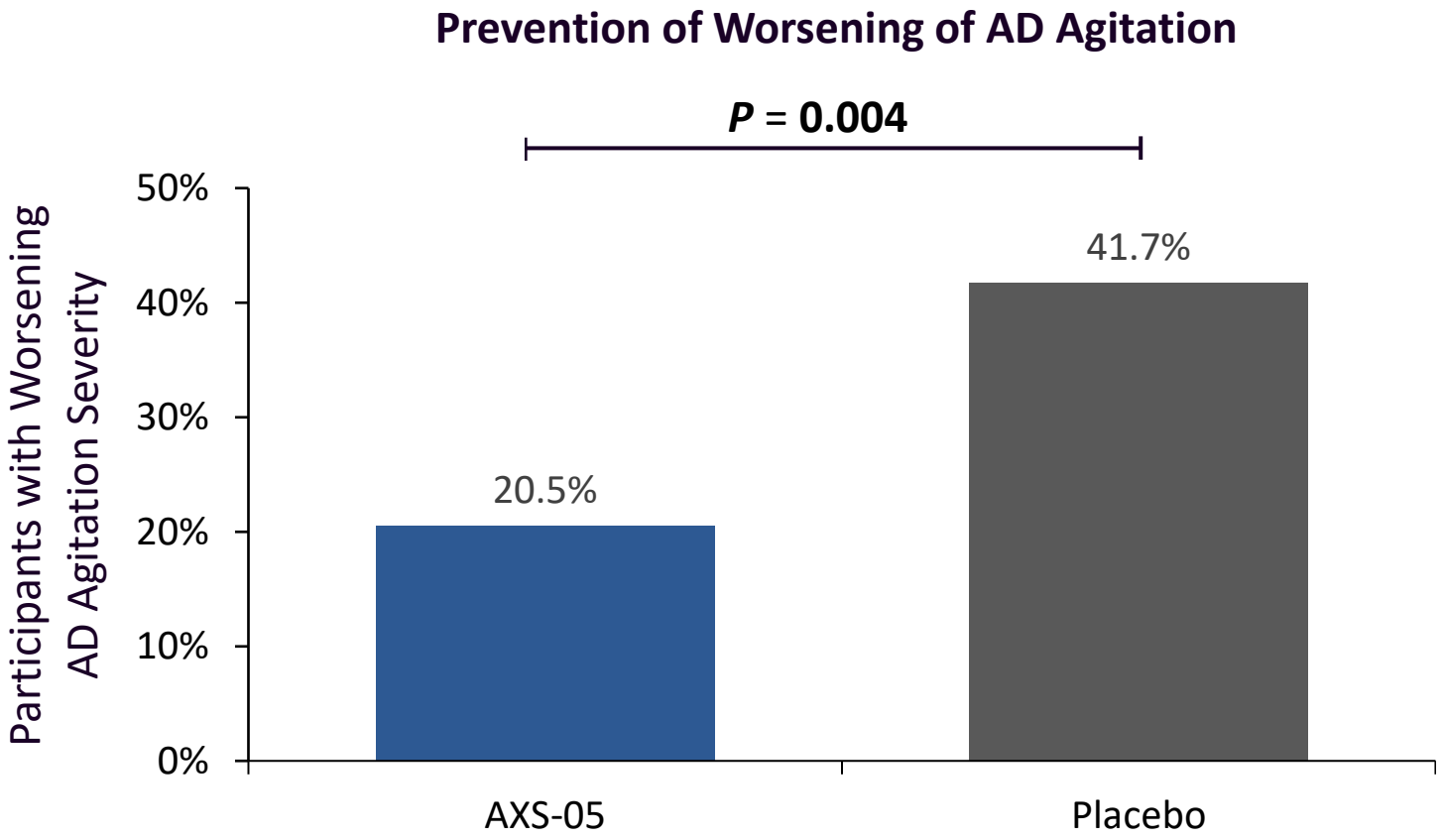
- AXS-05 met the key secondary endpoint by significantly preventing relapse of AD agitation compared to placebo (8.4% vs 28.6%; *P* = 0.001)



AD, Alzheimer's disease.

Efficacy: Secondary Endpoint – Decreased 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

- AXS-05 was well tolerated, with no new safety signals from previous studies
- 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 the MMSE
- No deaths were reported in either treatment group

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

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 for AD agitation with a novel mechanism of action

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