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

Authors: **Jeffrey Cummings**[1], George Grossberg[2], Caroline Streicher [3], Herriot Tabuteau[3]

[1]University of Nevada, Las Vegas - Las Vegas, NV, USA; [2]Saint Louis University School of Medicine – St. Louis, MO, USA; [3]Axsome Therapeutics - New York, NY, USA

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- **Dr. Jeffrey 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.

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INTRODUCTION

- Alzheimer's disease-related agitation (AD Agitation) is reported in up to 70% of people with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability and disinhibition[1,2]
- AD Agitation is associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality[3,4,5]
- Psychosocial interventions for AD Agitation, while recommended as first line therapy, are not always effective[3,5]
- In the ADVANCE-1 Phase 2/3 study, AXS-05 achieved the primary endpoint and significantly delayed relapse of agitation as measured by CMAI total score in patients with AD Agitation as compared to placebo[6]

CMAI, Cohen-Mansfield Agitation Inventory.

1. Tractenberg RE, et al. J Neuropsychiatry Clin Neurosci 2002;14(1):11-18. 2. Sano M, et al. Int Psychogeriatr 2023:1-13. 3. Porsteinsson AP, et al. Neurodegener Dis Manag 2014;4(5):345-349. 4. Rabins PV, et al. Alzheimers Dement 2013;9(2):204-207. 5. Lee D, et al. Expert Opin Pharmacother. 2023; 24(6):691-703. 6. O'Gorman, et al. CTAD 2020 Digital Conference, Nov 4-7, 2020.

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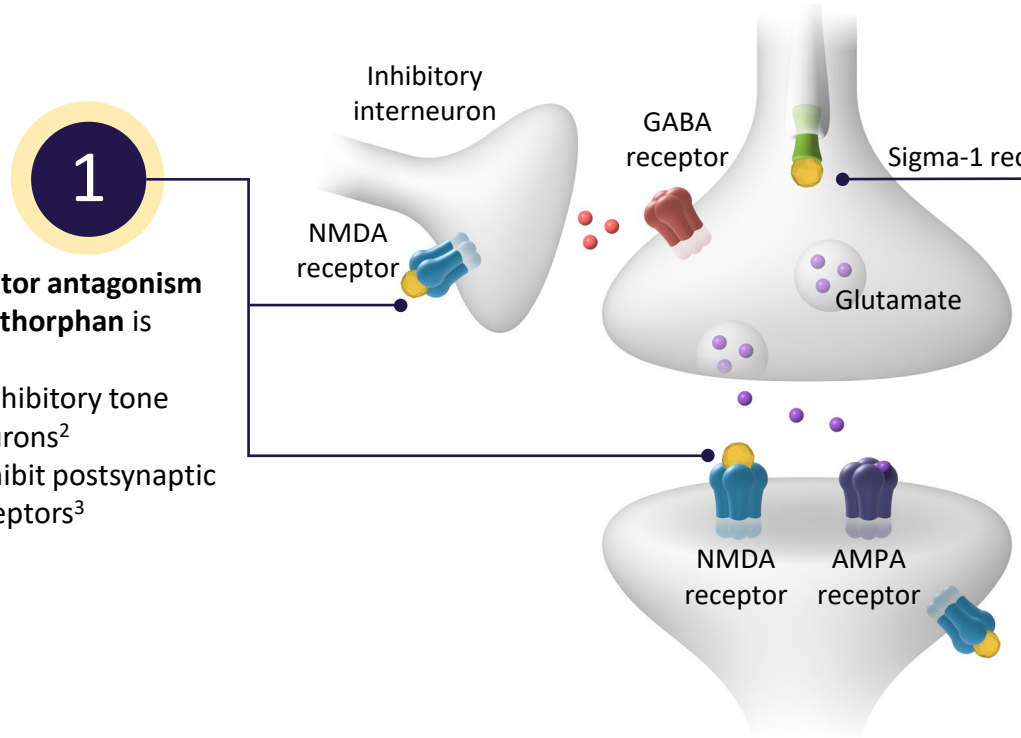
AXS-05: A NOVEL, ORAL NMDA RECEPTOR ANTAGONIST

- 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 MDD in adults[1]



NMDA receptor antagonism by dextromethorphan is believed to[1]:

- Alter the inhibitory tone of interneurons[2]
- Directly inhibit postsynaptic NMDA receptors[3]

Sigma-1 receptor agonism by dextromethorphan may additionally modulate glutamate and monoamine signaling[1,4]

Bupropion, a CYP2D6 inhibitor[1]:

- Increases and prolongs plasma concentrations of dextromethorphan
- Is a relatively weak inhibitor of norepinephrine and dopamine reuptake

Figure adapted from Kadriu B et al. Int J Neuropsychopharmacol. 2019;22(2):119-135.[5]
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA; gamma-aminobutyric acid; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate.
1. Auvelity [Prescribing Information]. Axsome Therapeutics, Inc.: New York, NY. 2. Duman RS et al. Nat Med. 2016;22(3):238-249. 3. Stahl SM. CNS Spectr. 2019;24(5):461-466. 4. Yang K et al. Front Pharmacol. 2019; 10:528. 5. Kadriu B et al. Int J Neuropsychopharmacol. 2019;22(2):119-135..

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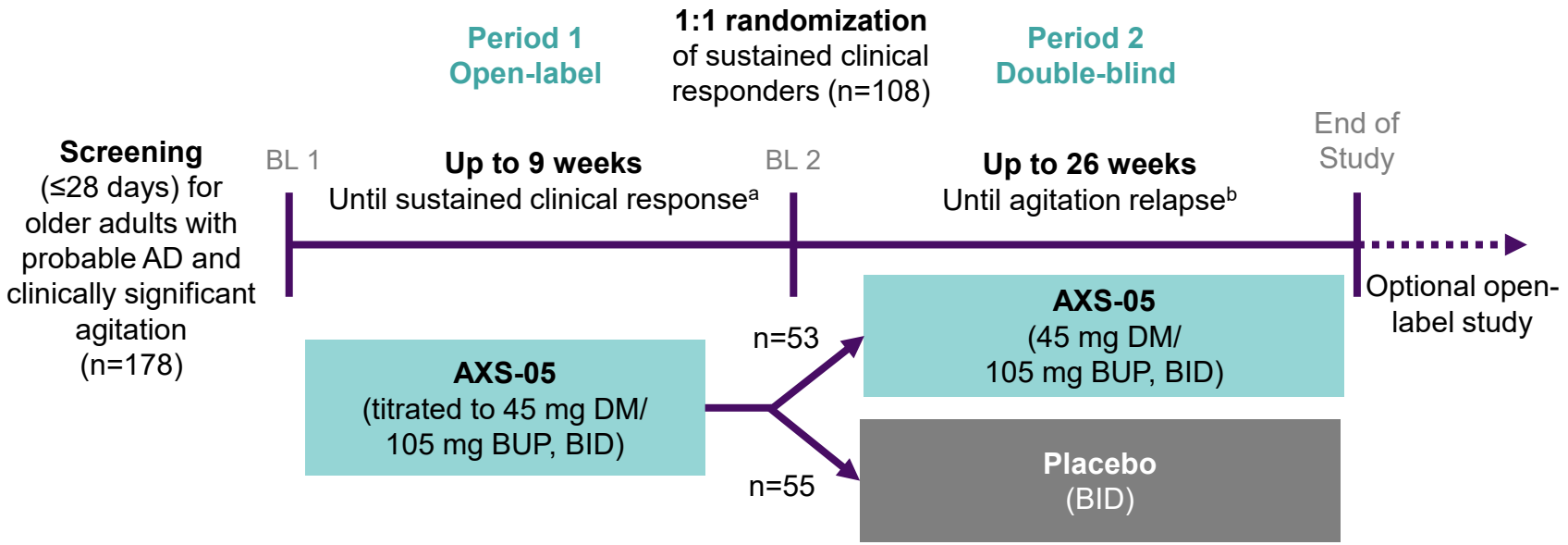
ACCORD RANDOMIZED DISCONTINUATION STUDY DESIGN

- The ACCORD (Assessing Clinical Outcomes in Alzheimer's Disease Agitation; NCT04797715) study 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
- The primary endpoint was time from randomization to relapse of agitation
- The key secondary endpoint was the 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 ADA.
AD, Alzheimer's disease; ADA, Alzheimer's disease-related agitation; BID, twice daily; BL, baseline; BUP, bupropion; CMAI, Cohen-Mansfield Agitation Inventory; DM, dextromethorphan; PGI-C, Patient Global Impression of Change.

INCLUSION AND EXCLUSION CRITERIA

- The study enrolled participants with probable AD and clinically significant agitation

Key Inclusion and Exclusion Criteria	
Inclusion	**Exclusion**
▪ Age 65-90 years (inclusive) ▪ Probable AD according to 2011 NIA-AA criteria ▪ Clinically significant agitation according to IPA provisional definition ▪ MMSE score 10-24 (inclusive) ▪ Care partner 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 investigator

AD, Alzheimer's disease; IPA, International Psychogeriatric Association; MMSE, Mini Mental State Examination; NIA-AA, National Institute of Aging-Alzheimer Association.
'Care partner' was captured as 'caregiver' during clinical trial execution.

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PARTICIPANT POPULATION

Demographics and Baseline Characteristics			
	Open-Label Period (Efficacy Population)	Double-Blind Period (ITT Population)	
	AXS-05 (n=178)	AXS-05 (n=53)	Placebo (n=55)
Demographics			
Age, years, mean (SD)	74.9 (6.0)	74.1 (6.0)	74.9 (6.2)
Women, n (%)	95 (53.4)	27 (50.9)	30 (54.5)
Race, n (%)			
White	152 (85.4)	45 (84.9)	47 (85.5)
Black	18 (10.1)	4 (7.5)	7 (12.7)
Asian	4 (2.2)	2 (3.8)	1 (1.8)
Other or not reported	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.

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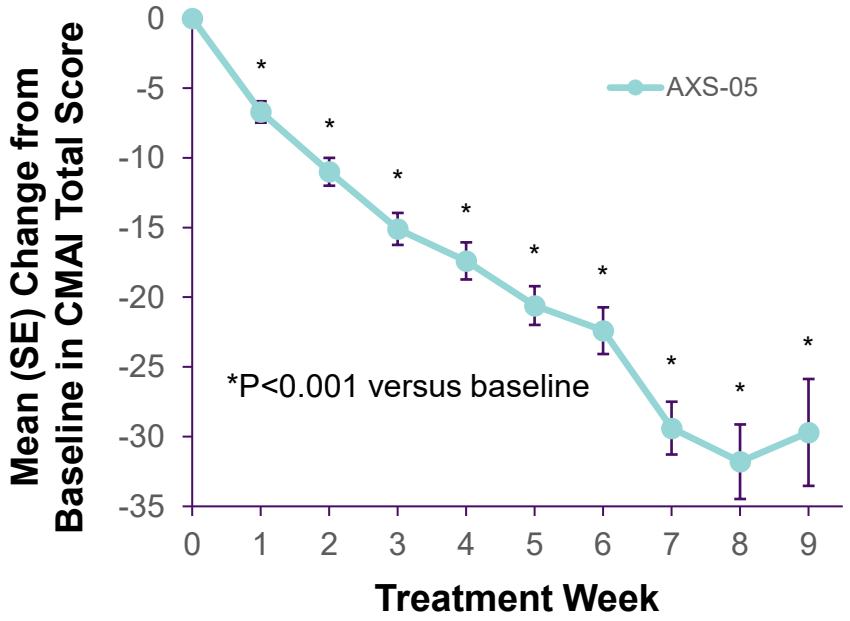
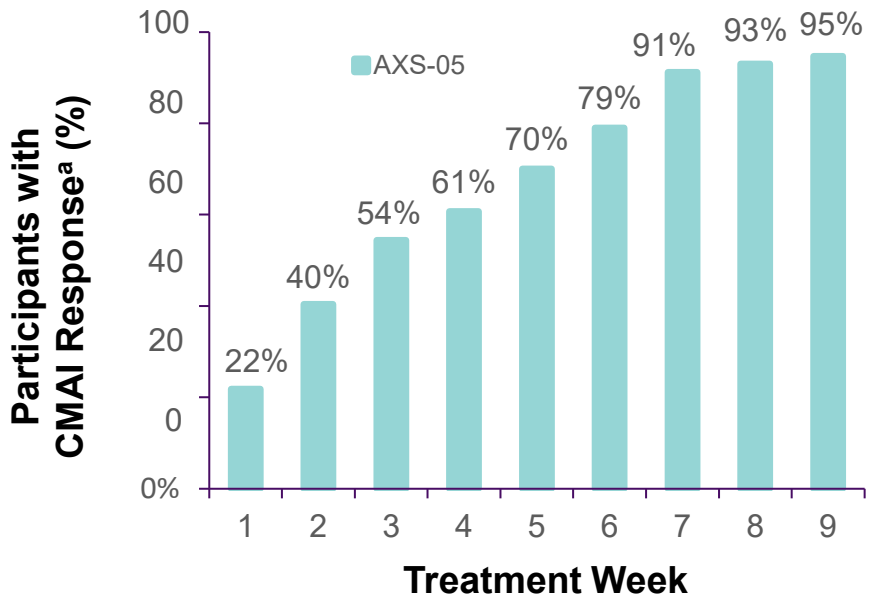
EFFICACY IN OPEN-LABEL PERIOD PRIOR TO RANDOMIZED DISCONTINUATION

- Statistically significant improvement compared to baseline in Cohen-Mansfield Agitation Inventory (CMAI) total score was observed at all timepoints starting at Week 1 with AXS-05 treatment
- Clinical response (≥30% CMAI reduction) was observed in nearly 80% of participants by Week 6

Open-Label Period CMAI Mean Change From Baseline



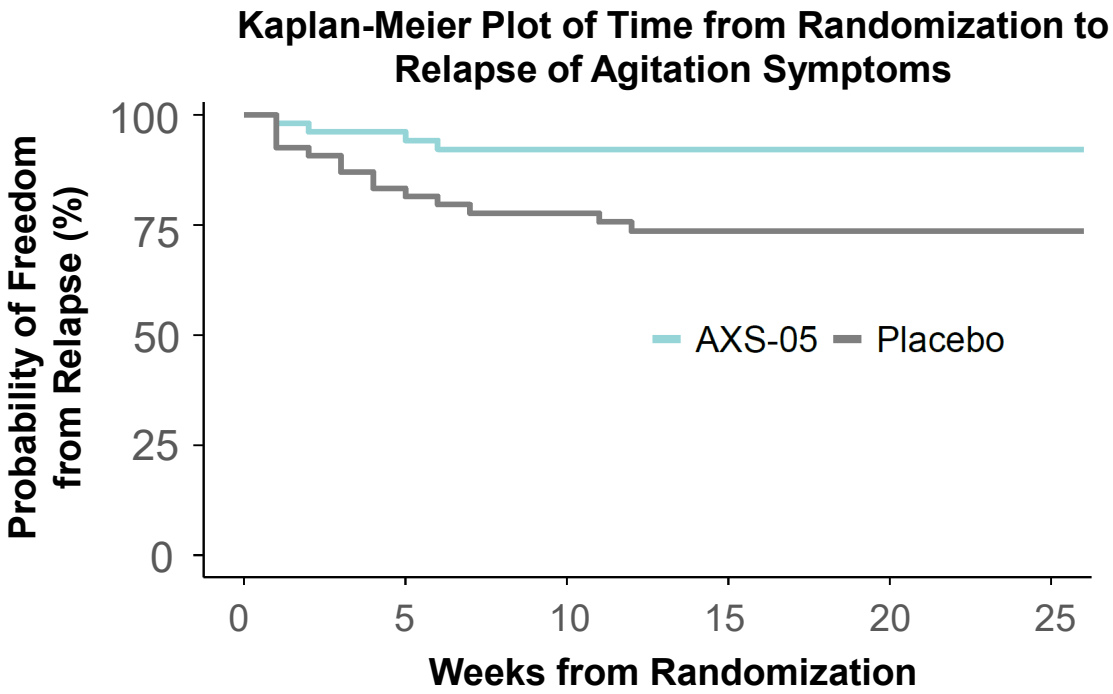
Clinical Response (≥30% Reduction) on CMAI



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

EFFICACY IN THE DOUBLE-BLIND PERIOD: TIME TO RELAPSE (PRIMARY ENDPOINT)

- AXS-05 substantially and statistically increased the time to relapse of agitation symptoms compared with placebo (Hazard ratio, 0.275; *P*=0.014)
- Risk of relapse was 3.6-fold less with AXS-05 compared with placebo



Agitation relapse defined as:

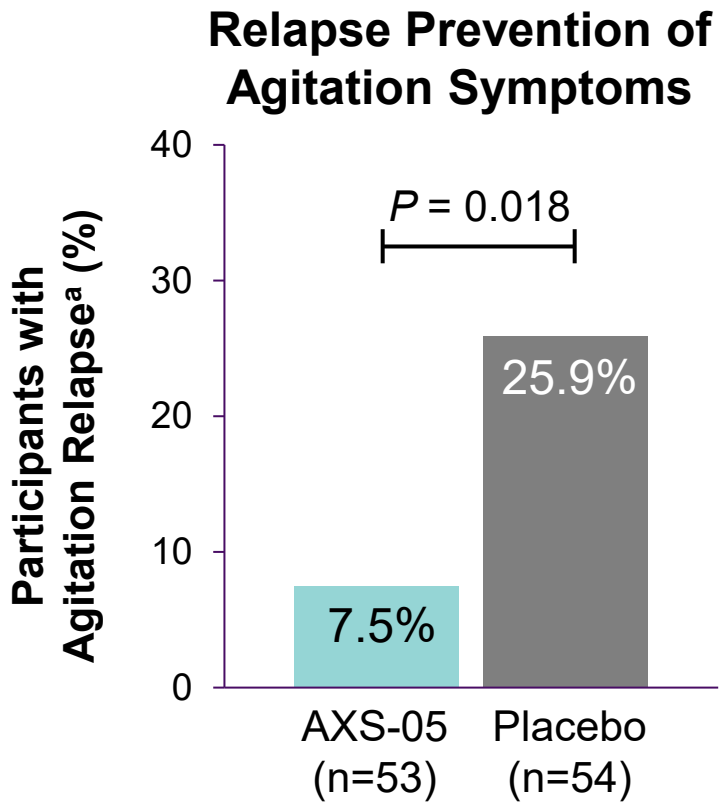
- A ≥10-point worsening in the CMA total score from randomization
- Or a CMAI total score greater than that at study entry
- Or hospitalization
- Or other institutionalization due to AD Agitation

Hazard Ratio for Time to Relapse	
Hazard Ratio (95% CI)	0.275 (0.091-0.836)
P-value	0.014

CMAI, Cohen-Mansfield Agitation Inventory; mITT, modified intent-to-treat.

EFFICACY IN THE DOUBLE-BLIND PERIOD: RELAPSE PREVENTION (KEY SECONDARY ENDPOINT)

- AXS-05 significantly prevented relapse compared with placebo (7.5% vs 25.9% of participants; *P*=0.018)



Agitation relapse defined as:

- A ≥10-point worsening in the CMA total score from randomization
- Or a CMAI total score greater than that at study entry
- Or hospitalization
- Or other institutionalization due to AD Agitation

[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.

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SAFETY

- Discontinuations in the double-blind period due to AEs were low (0% for AXS-05 and 1.9% for placebo)
- Three serious AEs were reported: 1 in the AXS-05 group (faecaloma), which was not attributed to study medication, and 2 in the placebo group (cardiac arrest, femur fracture)
- 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
- One death was reported in the placebo group
- There was no evidence of cognitive decline with AXS-05 as shown by the MMSE
- Treatment with AXS-05 was not associated with sedation.

Summary of Treatment-Emergent Adverse Events

n (%)	Double-Blind Period (Safety Population[a])	
	AXS-05 (n=53)	Placebo (n=54)
Participant with ≥1 TEAE	15 (28.3)	12 (22.2)
Serious TEAE	1 (1.9)	2 (3.7)
Drug-related TEAE	3 (5.7)	2 (3.7)
Participant with TEAE leading to		
Study discontinuation	0	1 (1.9)
Death	0	1 (1.9)[b]
Most common TEAE (≥5% in any group)[c]		
Dizziness	0	1 (1.9)
Fall	4 (7.5)	2 (3.7)
Diarrhea	4 (7.5)	2 (3.7)
Back pain	3 (5.7)	2 (3.7)

[a]Safety Population includes all subjects who receive at least 1 dose of AXS-05. [b]Death due to cardiac arrest; [c]TEAEs reported by preferred term.
MMSE, Mini Mental State Examination; TEAE, treatment-emergent adverse event.

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CONCLUSIONS

- AXS-05 significantly delayed time to relapse and prevented more relapses of AD Agitation compared to placebo in the ACCORD study (primary outcome)
- Treatment with AXS-05 during the open-label period resulted in rapid and clinically meaningful improvements in AD Agitation
- AXS-05 was generally safe and well tolerated in the trial
- AXS-05 was not associated with cognitive impairment or sedation
- The efficacy and safety results with AXS-05 support its potential to fulfill a high unmet need for the treatment of AD Agitation

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AD Agitation, Alzheimer's disease-related agitation.