Clinical Profile of AXS-05 (Dextromethorphan-Bupropion) in Treating Alzheimer's Disease Agitation: Results From The Phase 2/3 Development Program

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Key Objective

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

Conclusions

- AXS-05 was associated with a substantial, rapid reduction in AD agitation compared with controls after 5 weeks of treatment
- In ACCORD longer-term treatment with AXS-05 significantly increased the time to relapse of AD agitation and reduced the risk of relapse
- AXS-05 was generally well tolerated across studies, further supporting the continued development of AXS-05 as a promising treatment option for AD agitation

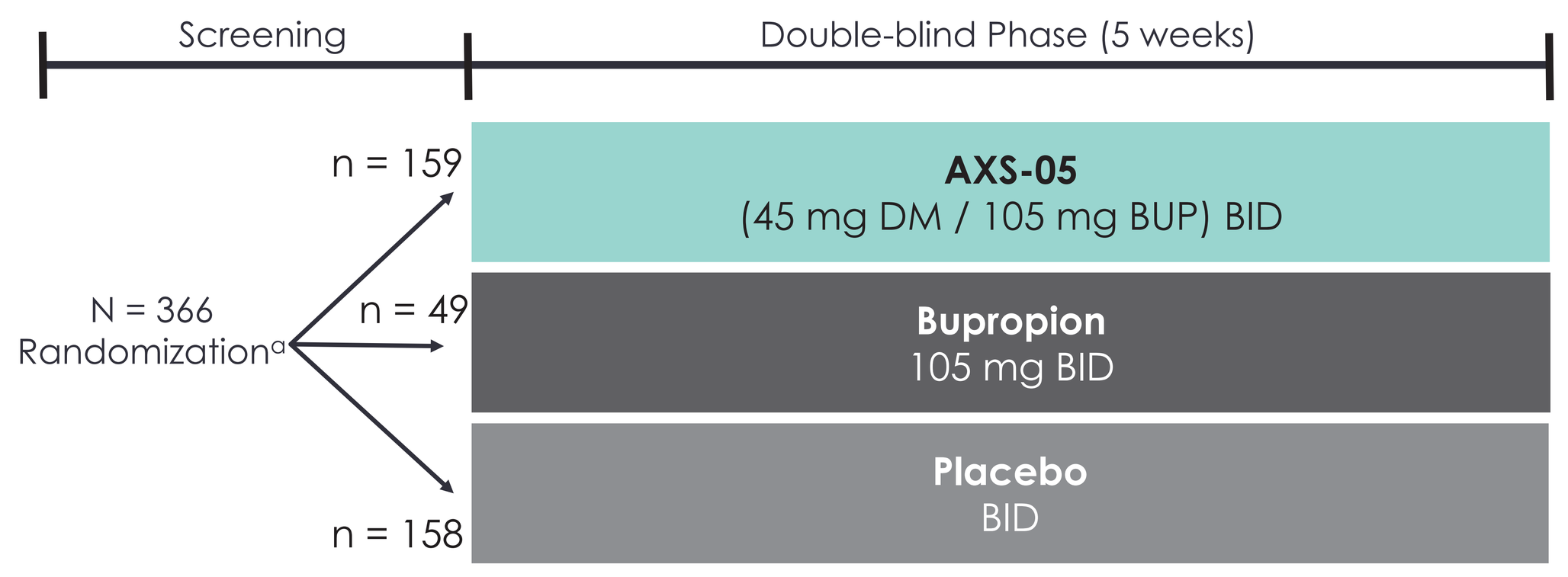
Introduction

- Alzheimer's disease-related agitation (AD Agitation) is reported in up to 70% of people with Alzheimer's disease and is characterized by emotional distress, aggressive behavior, 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]
- Non-pharmacological therapies for AD Agitation, while recommended as first-line therapy, are not always effective[3,5]
- 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[6]

Methods & Study Design

ADVANCE-1

- The ADVANCE-1 (Addressing Dementia via Agitation-Centered Evaluation 1; NCT03226522) study was a Phase 2/3 randomized, double-blind, controlled study to evaluate the efficacy and safety of AXS-05 in patients with AD agitation



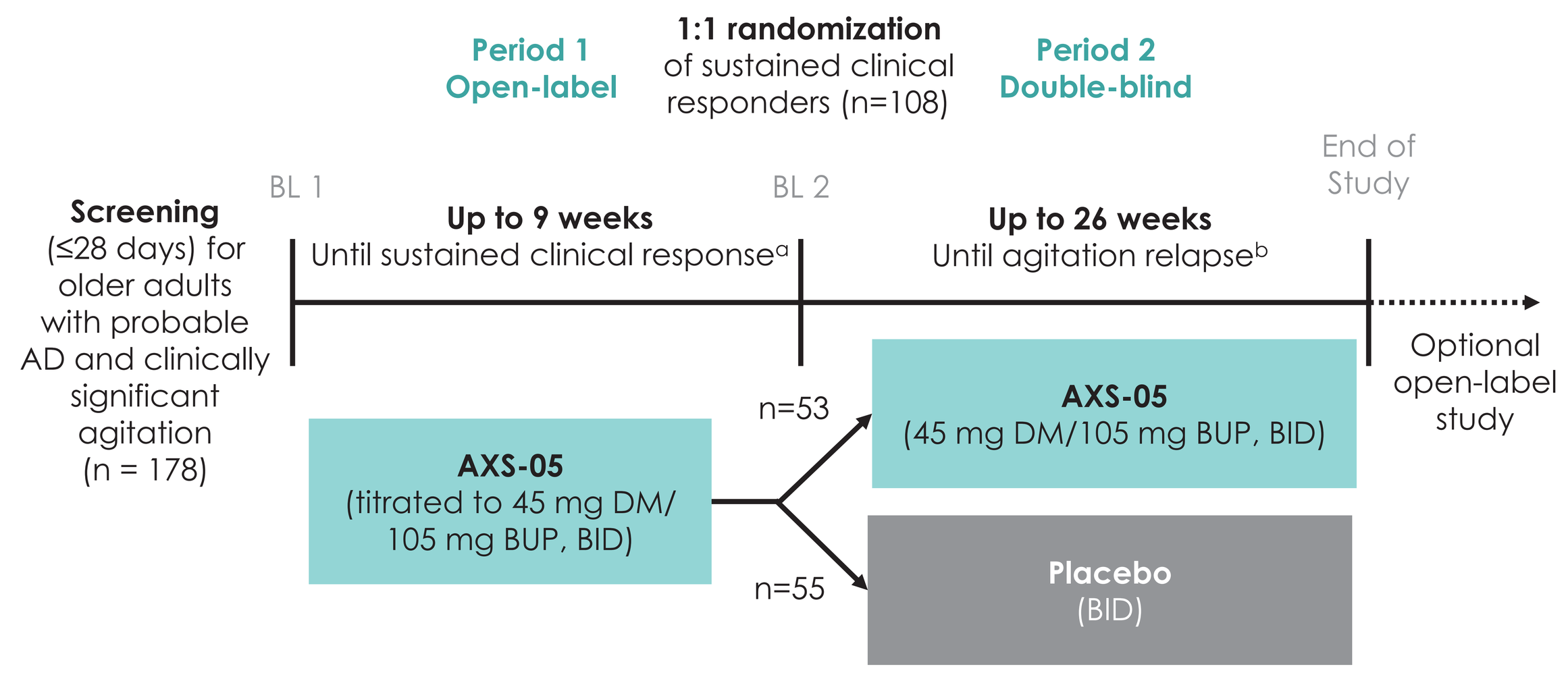
[a]An independent data monitoring committee performed an interim futility analysis and recommended no further randomization to the bupropion arm. Subsequently, patients were randomized in a 1:1 ratio to receive AXS-05 or placebo
BID, twice daily; BUP, Bupropion; DM, Dextromethorphan.

Primary endpoint: Change from baseline to Week 5 in the Cohen-Mansfield Agitation Inventory (CMAI) total score

Dose titration:
- Week 1: AXS-05 (30 mg DM/105 mg BUP) once daily
- Week 2: AXS-05 (30 mg DM/105 mg BUP) twice daily
- Weeks 3-5: AXS-05 (45 mg DM/105 mg BUP) twice daily

ACCORD

- 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



[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-related agitation; BID, twice daily; BL, baseline; BUP, bupropion; CMAI, Cohen-Mansfield Agitation Inventory; DM, dextromethorphan; PGI-C, Patient Global Impression of Change

Primary endpoint: Time from randomization to relapse of agitation
Key secondary endpoint: Percentage of participants who relapsed

Table 1. ADVANCE-1 and ACCORD Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
• Age 65-90 years (inclusive)	• Predominantly non-AD dementia
• Probable AD according to 2011 NIA-AA criteria[7]	• Agitation symptoms not secondary to AD
• Agitation according to IPA provisional definition[8]	• Concurrent medical condition that may interfere with study conduct
• MMSE score 10-24 (inclusive)[a]	• Medically inappropriate in opinion of investigator
• NPI-AA score ≥ 4	• Current use of SSRI/SNRI (ADVANCE-1)
• Community-dwelling (ADVANCE-1)	
• Caregiver participation (ACCORD)	

[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.

Key Findings

Patient Population

Table 2. Demographics and Baseline Characteristics

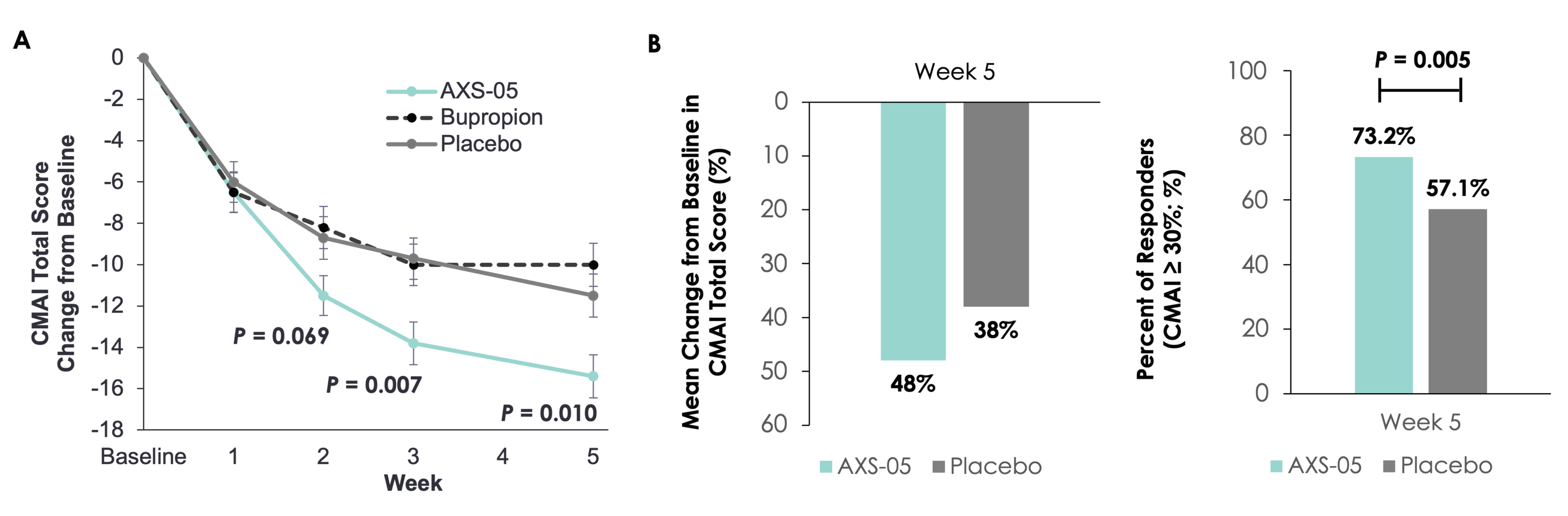
	ADVANCE-1			ACCORD Open-Label Period	ACCORD Double-Bind Period	
	AXS-05 (n = 152)	Bupropion (n = 49)	Placebo (n = 156)	AXS-05 (n = 178)	AXS-05 (n = 53)	Placebo (n = 55)
Age, years, mean (SD)	75.2 (5.71)	76.4 (6.13)	75.1 (5.96)	74.9 (6.0)	74.1 (6.0)	74.9 (6.2)
Female Gender, n (%)	86 (56.6)	22 (44.9)	91 (58.3)	95 (53.4)	27 (50.9)	30 (54.5)
Race, n (%)						
White	136 (89.5)	43 (87.8)	128 (82.1)	152 (85.4)	45 (84.9)	47 (85.5)
Black or African American	11 (7.2)	5 (10.2)	25 (16.0)	18 (10.1)	4 (7.5)	7 (12.7)
Asian	1 (0.7)	0	1 (0.6)	4 (2.2)	2 (3.8)	1 (1.8)
Other	4 (2.6)	1 (2.0)	2 (1.3)	4 (2.2)	2 (3.8)	0
CMAI total score, mean (SD)	60.7 (17.40)	66.1 (19.65)	59.4 (15.60)	70.9 (22.3)	43.7 (10.2)	44.9 (10.9)
NPI-AA total score, mean (SD)[a]	7.2 (2.17)	6.9 (2.45)	6.8 (2.07)	7.0 (2.0)	4.1 (2.0)	3.6 (1.9)
CGI-S agitation, mean (SD)	4.2 (0.77)	4.4 (0.82)	4.2 (0.65)	4.3 (0.6)	2.7 (0.8)	2.9 (0.8)
MMSE total score, mean (SD)	18.7 (3.76)	17.8 (4.19)	18.8 (3.70)	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.

- Baseline and sociodemographic characteristics were generally similar across AXS-05 and control groups in their respective studies

ADVANCE-1 Efficacy

Figure 2. Change in CMAI Total Score (A), Clinically Meaningful Improvement (B), and Clinical Response (C)

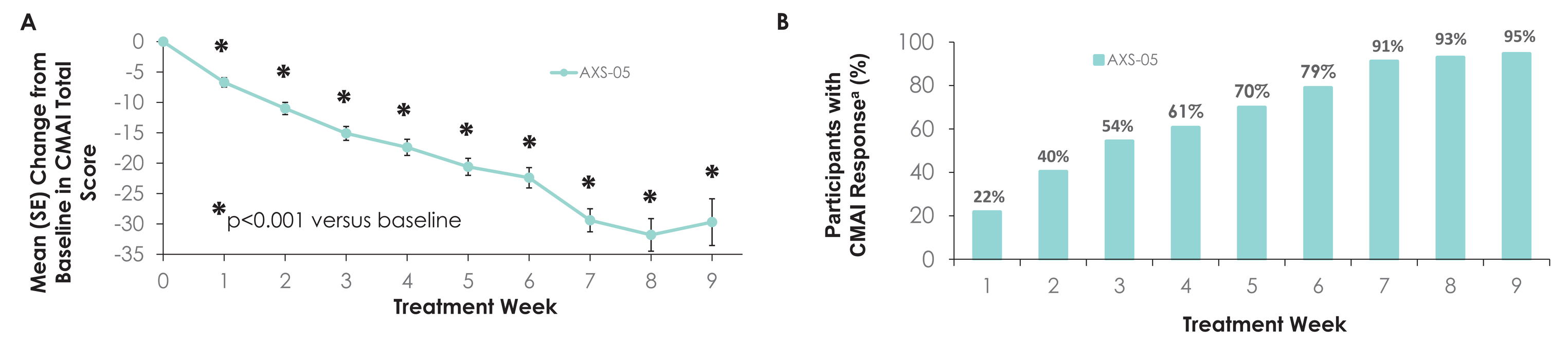


*P-values are calculated from LS mean
CMAI, Cohen-Mansfield Agitation Inventory.

- AXS-05 demonstrated a statistically significant mean reduction in the CMAI total score compared to placebo at Week 5, with mean reductions from baseline of 15.4 points for AXS-05 and 11.5 points for placebo ($P = 0.010$); AXS-05 also demonstrated statistical separation from bupropion on the CMAI total score ($P < 0.001$; **Figure 2A**)
- At Week 5, AXS-05 reduced CMAI total score from baseline by a mean percentage of 48% for AXS-05 versus 38% for placebo (**Figure 2B)**
- A statistically significantly greater proportion of patients achieved a clinical response (≥ 30% improvement from baseline) on the CMAI with AXS-05 as compared to placebo (73.2% versus 57.1%, $P = 0.005$; **Figure 2C**)

ACCORD Efficacy

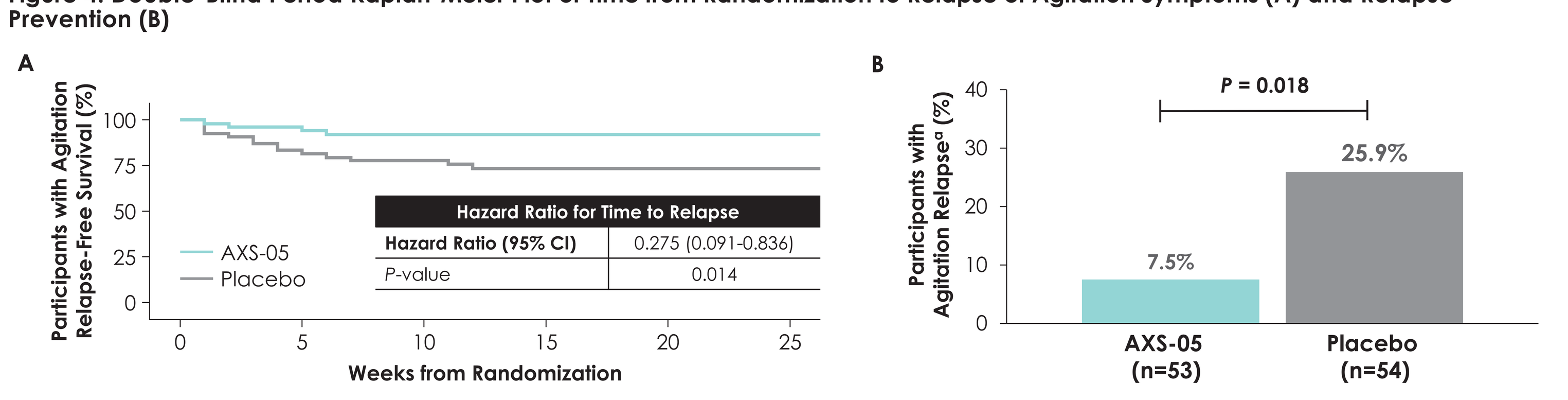
Figure 3. Open-Label Period CMAI Mean Change From Baseline (A) and Clinical Response (≥30% Reduction) on CMAI (B)



[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 3A**)
- Clinical response (≥30% CMAI reduction) was observed in nearly 80% of participants by Week 6 (**Figure 3B**)

Figure 4. 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 4A**); risk of relapse was 3.6-fold lower with AXS-05 compared with placebo
- AXS-05 significantly prevented relapse compared with placebo (7.5% vs 25.9% of participants; $P = 0.018$; **Figure 4B**)

Safety

Table 3. Summary of Treatment-Emergent Adverse Events

	ADVANCE-1			ACCORD Double-Blind Period[a]	
n (%)	AXS-05 (n = 159)	Bupropion (n = 49)	Placebo (n = 158)	AXS-05 (n = 53)	Placebo (n = 55)
Participant with ≥1 TEAE[b]	70 (44.0)	30 (61.2)	52 (32.9)	15 (28.3)	12 (22.2)
Serious TEAE	5 (3.1)	4 (8.2)	9 (5.7)	1 (1.9)	2 (3.7)
Participant with TEAE leading to study discontinuation	2 (1.3)	1 (2.0)	2 (1.3)	0	1 (1.9)
Participant with TEAE leading to death	0	1 (2.0)	1 (0.6)	0	1 (1.9)[c]

[a]Safety Population includes all subjects who receive at least 1 dose of AXS-05. [b]During the ACCORD 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.

- In ADVANCE-1, the most commonly reported adverse events (AXS-05, bupropion, and placebo, respectively) in the AXS-05 arm were somnolence (8.2%, 4.1%, and 3.2%), dizziness (6.3%,10.2%, and 3.2%), and diarrhea (4.4%, 6.1%, and 4.4%)
- In ACCORD, 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

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