

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)

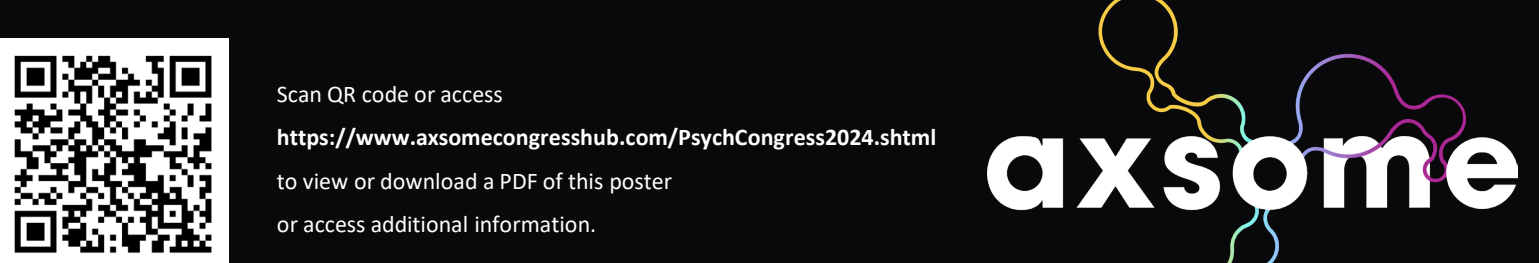
Conclusions

- 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

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Disclosures
 J. Cummings has provided consultation to Acadia, Acumen, AlZaeth, Amnovo, Aprinista, Artery, Axsome Therapeutics, Biogen, Biohaven, Biocxel, Bristol-Myers Squibb, Eisai, Fosun, GAP Foundation, Green Valley, Janssen, Karuna, Kinosis, Lighthouse, Lilly, Lundbeck, LSP/eet, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optocue, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Sincere, Sinapica, TrueBinding, and Vaxxinity pharmaceutical, assessment and investment companies. He is supported by US National Institute of General Medical Sciences (NIGMS) grant P20GM09925, National Institute on Aging (NIA) grant R50AG071476, NIA grant R25 AG083721-01, the Alzheimer's Disease Drug Discovery Foundation (ADDF), the Ted and Maria Quirk Endowment, and the Jay Chambers-Grundy Endowment. G. Grossberg has provided consultation to Acadia, Alkermes, Avanir, Axovant, Axsome Therapeutics, Biogen, Biocxel, 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, IntracellularTherapeutics, Merck, Newton, and Oligomerix.
 C. Streicher, C. Zeni, and H. Tabuteau are current employees of Axsome Therapeutics.

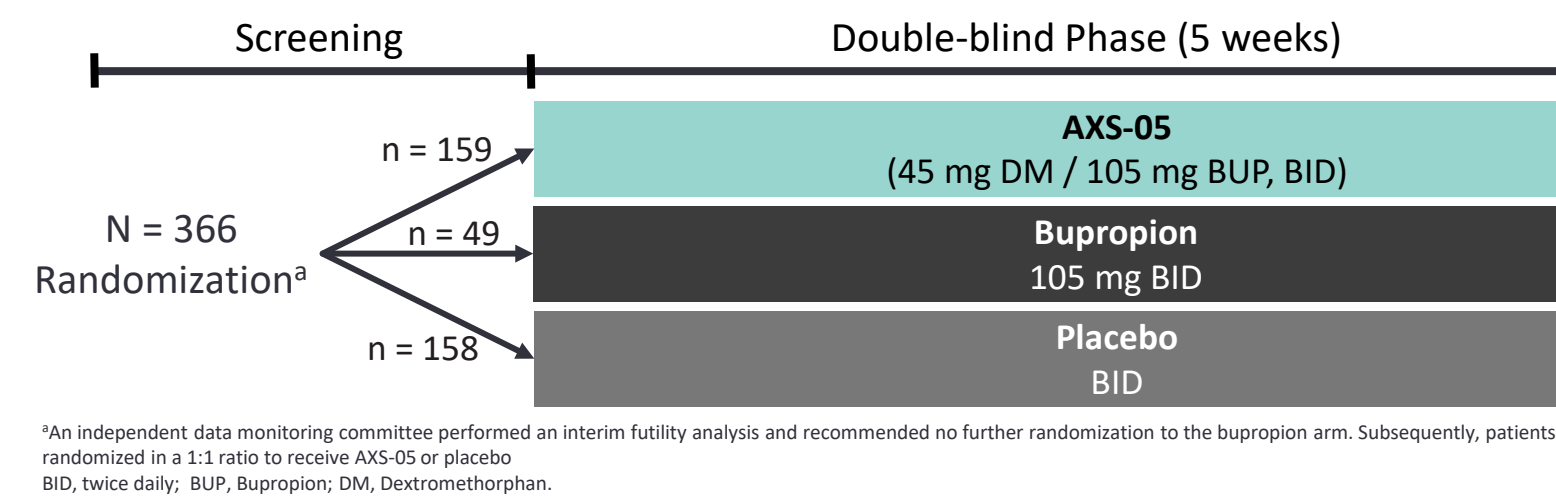


Introduction

- Alzheimer's disease 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 adults⁶

Methods & Study Design

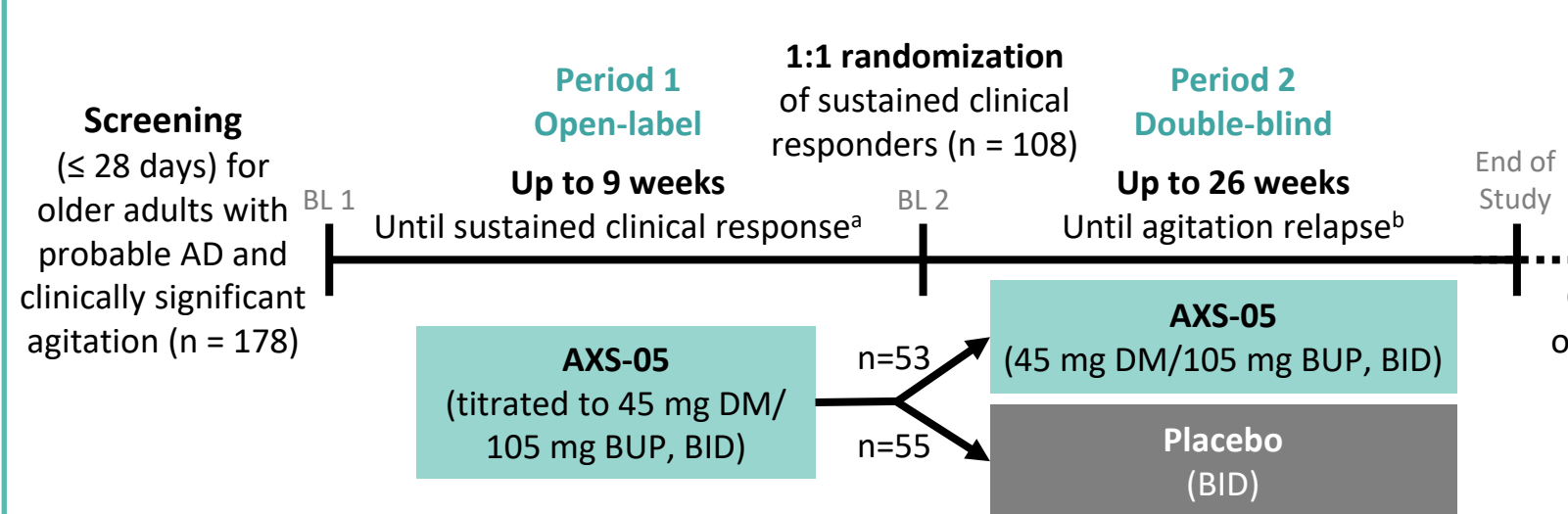
ADVANCE-1
 The ADVANCE-1 (Addressing Dementia via Agitation-Centered Evaluation 1; NCT03226522) study was a Phase 2/3 randomized, double-blind, controlled study to evaluate the efficacy and safety of AXS-05 in patients with AD agitation



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



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

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

^aAn 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

	ADVANCE-1			ACCORD		
	AXS-05 (n = 152)	Bupropion (n = 49)	Placebo (n = 156)	Open-Label Period (AXS-05 (n = 178))	Double-Bind Period (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)

^aNPI-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

ACCORD Efficacy

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

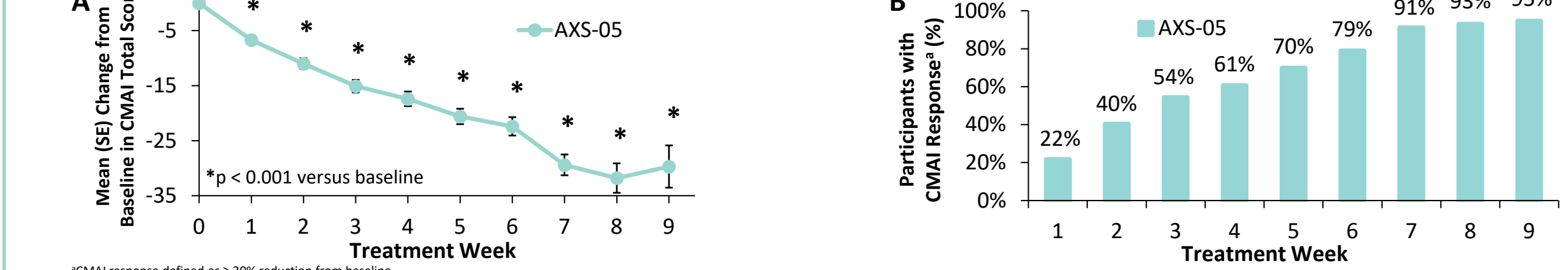
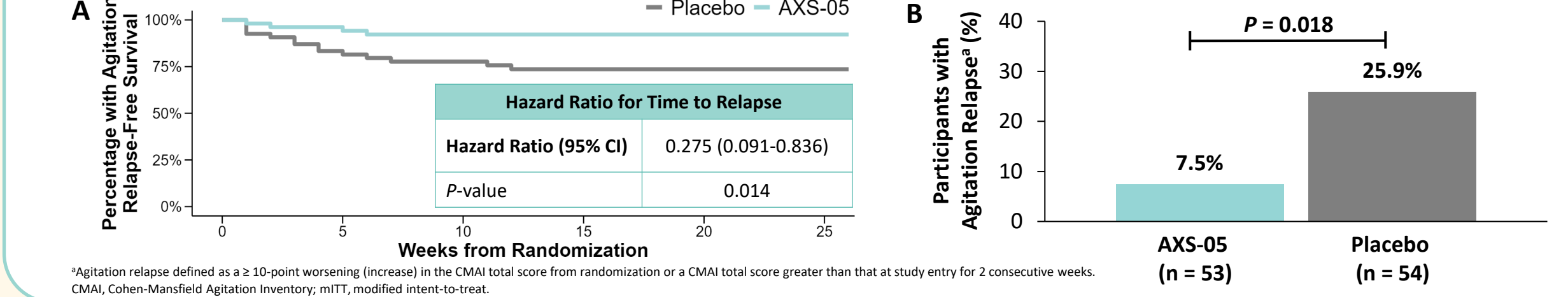
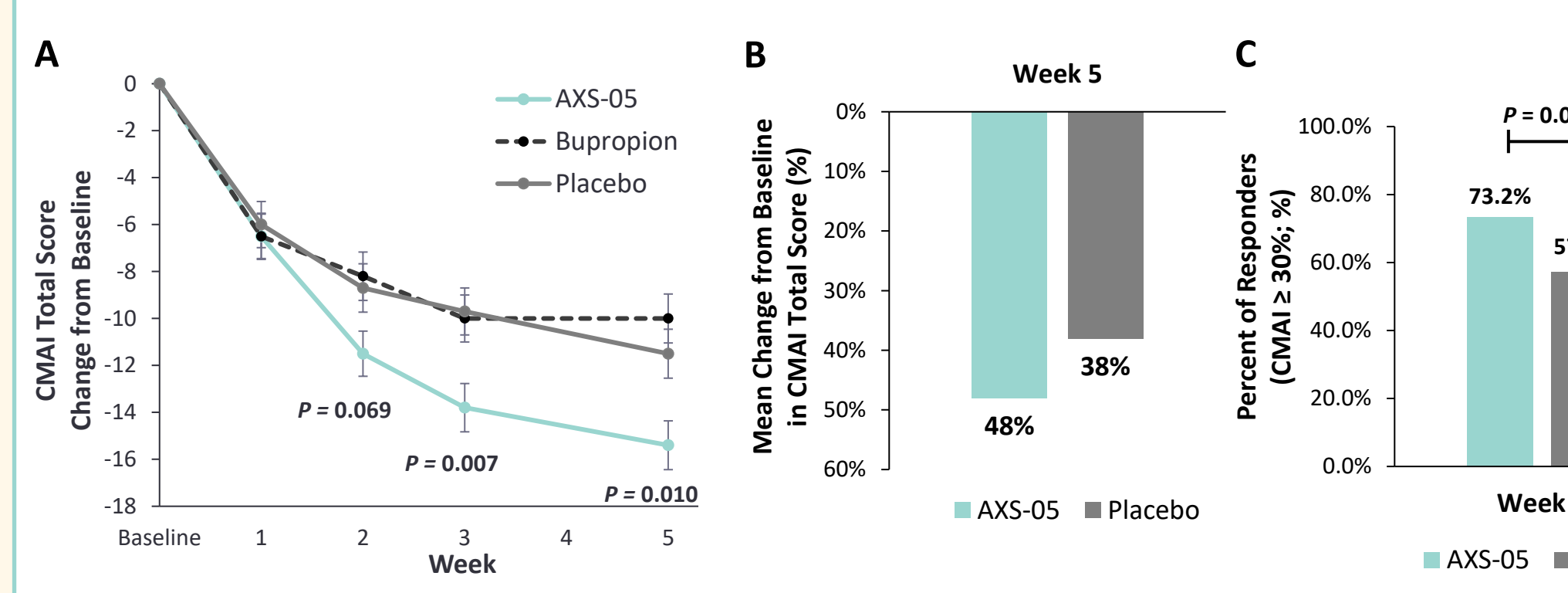


Figure 4. Double-Blind Period Kaplan-Meier Plot of Time from Randomization to Relapse of Agitation Symptoms (A) and relapse prevention (B)



ADVANCE-1 Efficacy

Figure 2. Change in CMAI total score (A), clinically meaningful improvement (B), and clinical response (C)



^aP-values are calculated from LS mean CMAI, Cohen-Mansfield Agitation Inventory.

ADVANCE-1 Efficacy

- 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**)

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

^aSafety Population includes all subjects who receive at least 1 dose of AXS-05. ^bDuring 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. ^cDeath due to cardiac arrest. MMSE, Mini Mental State Examination; TEAE, treatment-emergent adverse event.

- 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**)

- 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**)