NASDAQ: AXSM

AXSOME THERAPEUTICS

ADVANCE-1 Phase 2/3 Trial of AXS-05 in Alzheimer's Disease Agitation

Topline Results

Conference Call

April 27, 2020

AXS-05 in Alzheimer's Disease (AD) Agitation
ADVANCE-1 Phase 2/3 Trial Topline Results

Introduction	**Mark Jacobson**, Chief Operating Officer
Overview and Summary	**Herriot Tabuteau, MD**, Chief Executive Officer
ADVANCE-1 Trial Design & Results	**Cedric O'Gorman, MD**, Senior Vice President, Clinical Development & Medical Affairs
Q&A	**Presenters, Nick Pizzie**, Chief Financial Officer and **Dave Marek,** Chief Commercial Officer
Concluding Remarks	**Herriot Tabuteau, MD**, Chief Executive Officer

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Summary and Overview

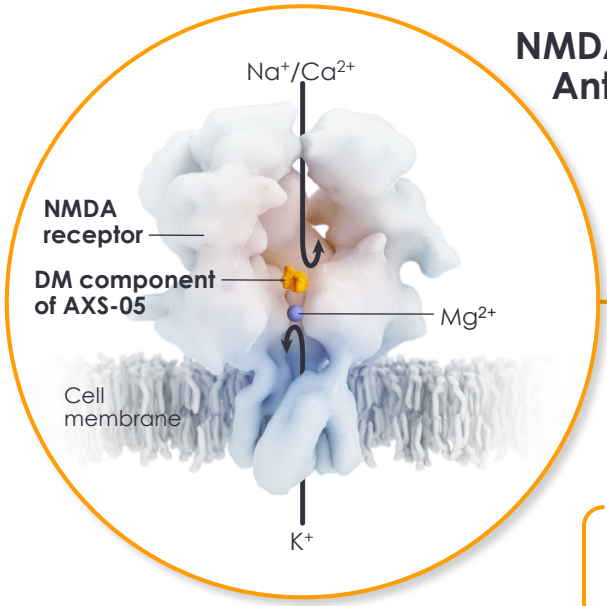
Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

Summary of AXS-05 ADVANCE-1 Topline Results: Significant Improvement in Alzheimer's Disease Agitation

- AXS-05: a novel, oral, investigational NMDA receptor antagonist with multimodal activity
- Achieved primary endpoint – rapid, substantial, and statistically significant improvements in CMAI total score versus placebo
- Component contribution established – AXS-05 statistically superior to bupropion at Week 5
- Clinically meaningful improvement in agitation
  - Almost 50% reduction from baseline in agitation symptoms
  - Achieved statistical significance in mADCS-CGIC
  - Significantly greater rates of clinical response on the CMAI, defined as a 30% or greater improvement, with AXS-05
- AXS-05 was generally safe, well tolerated, and was not associated with cognitive impairment or sedation
- No treatment currently approved for Alzheimer's disease agitation

AXS-05: Novel, Oral, NMDA Receptor Antagonist with Multimodal Activity

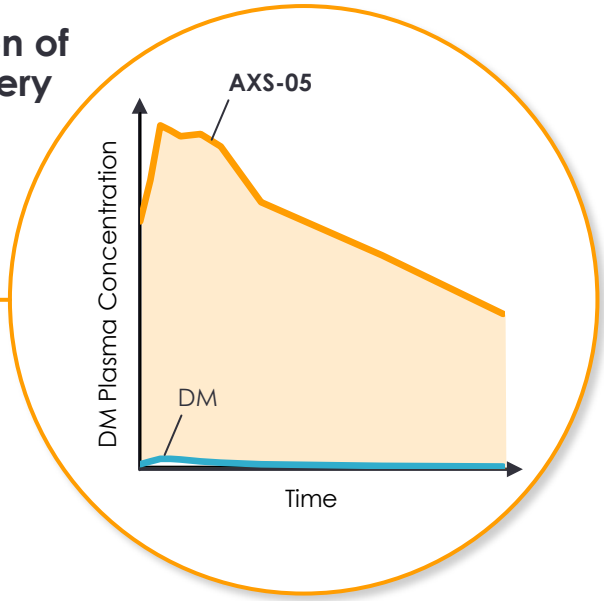


NMDA Receptor Antagonism

AXS-05

dextromethorphan/bupropion
modulated delivery tablet

Modulation of DM Delivery



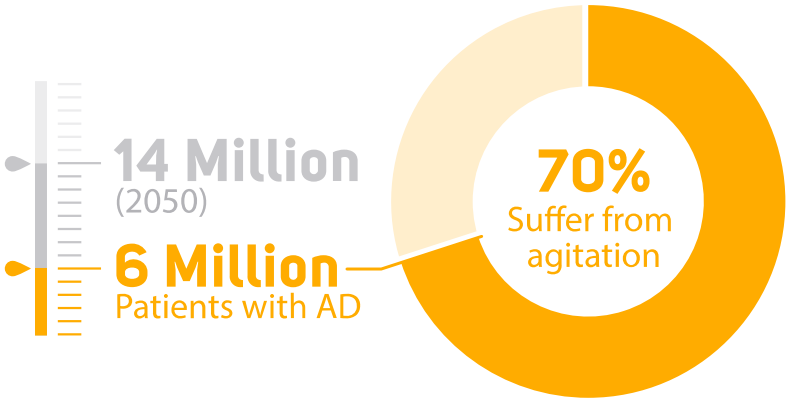
Sigma-1 Receptor Agonism

5-HT, NE, DA Reuptake Inhibition

Abbreviations: DM = Dextromethorphan; 5-HT = Serotonin; NE = Norepinephrine; DA = Dopamine; Mg2+ = magnesium ion; Na+ = sodium ion; Ca+2=calcium ion; K+=potassium ion.
Axsome data on file

Alzheimer's Disease Agitation: High Unmet Medical Need

- Alzheimer's disease (AD) is the most common form of dementia and is characterized by cognitive decline and behavioral symptoms including agitation[1,2]
- Agitation is seen in up to 70% of AD patients[2]:
  - Emotional distress, aggressive behaviors, disruptive irritability, and disinhibition
- Managing agitation is a major priority in AD[3,4]:
  - Associated with accelerated cognitive decline, earlier nursing home placement, and increased mortality risk
- No approved medication = high unmet medical need:
  - Off-label treatments (antipsychotics) not effective, and carry FDA black-box warnings against use in dementia due to increased risk of cerebrovascular events and death[3]

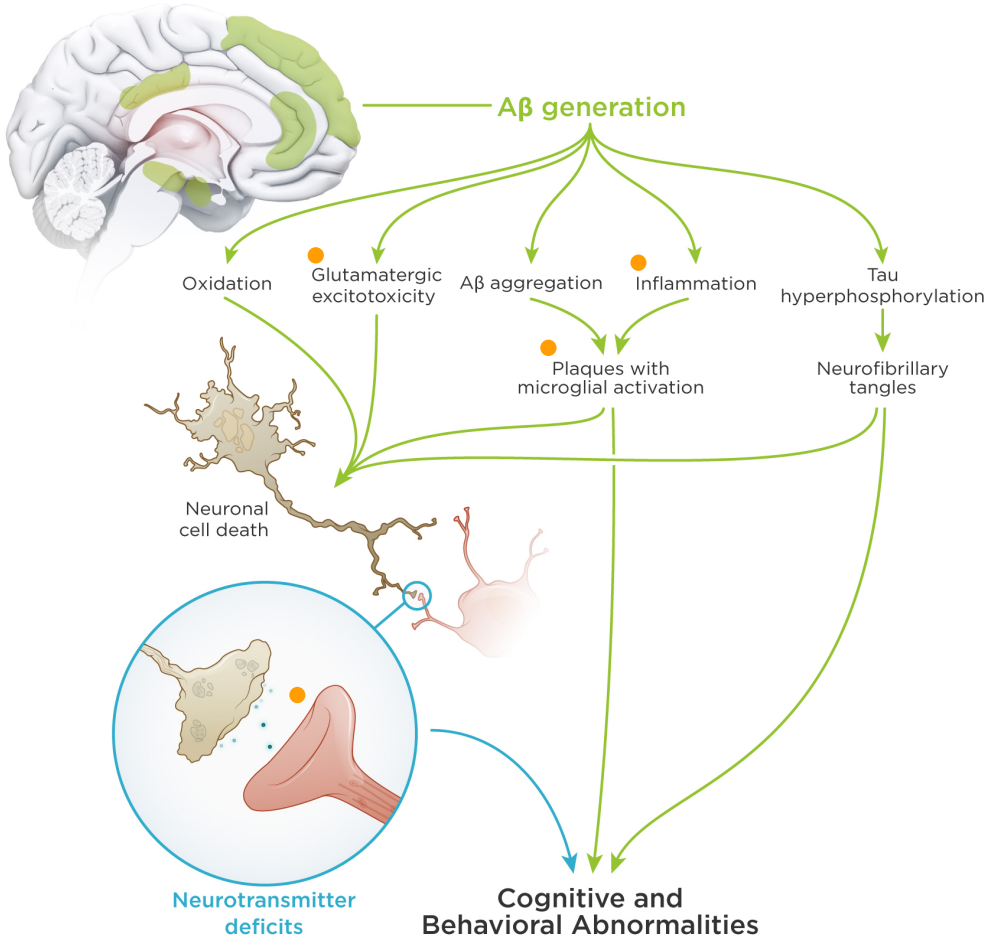


[1]Alzheimer's Association. *Alzheimers Dement.* 2020;16(3):391+. [2]Tractenberg R, et al. *J Neuropsychiatry Clin Neurosci.* 2002;14:11-18.
[3]Porsteinsson AP, et al. *Expert Opin Pharmacother.* 2017; 18:6, 611-620. [4]Rabins PV et al. *Alzheimers Dement.* 2013; 9:204-207.

Alzheimer's Disease:
Cognitive and Behavioral Symptom Mechanisms

- In Alzheimer's disease (AD), insoluble Aβ production and accumulation triggers secondary steps leading to synaptic loss and neuronal cell death, and a decrease in specific neurotransmitters[1,2]
- Neurotransmitter alterations in AD are thought to contribute to cognitive and behavioral symptoms including agitation and aggression[1-4]
- AXS-05 modulates the function of neurotransmitters (serotonin, glutamate, sigma-1, norepinephrine, and dopamine) implicated in AD[1-4]

Brain regions implicated in AD agitation[4]



● AXS-05 pharmacological actions[5,6]

[1]Cummings JL. *N Engl J Med*. 2004;351:56-67
[2]Querfurth HW, et al. *N Engl J Med*. 2010;362:329-44
[3]Porsteinsson AP, et al. *Expert Opin Pharmacother*. 2017; 18:6, 611-620
[4]Rosenberg PB, et al. *Mol Aspects Med*. 2015;0: 25–37
[5]Stahl SM. *CNS Spectr*. 2019;24:461-466
[6]Cheng W, et al. Mol Med Rep. 2015 Feb;11(2):1132-8

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ADVANCE-1 Phase 2/3 Trial Design & Results

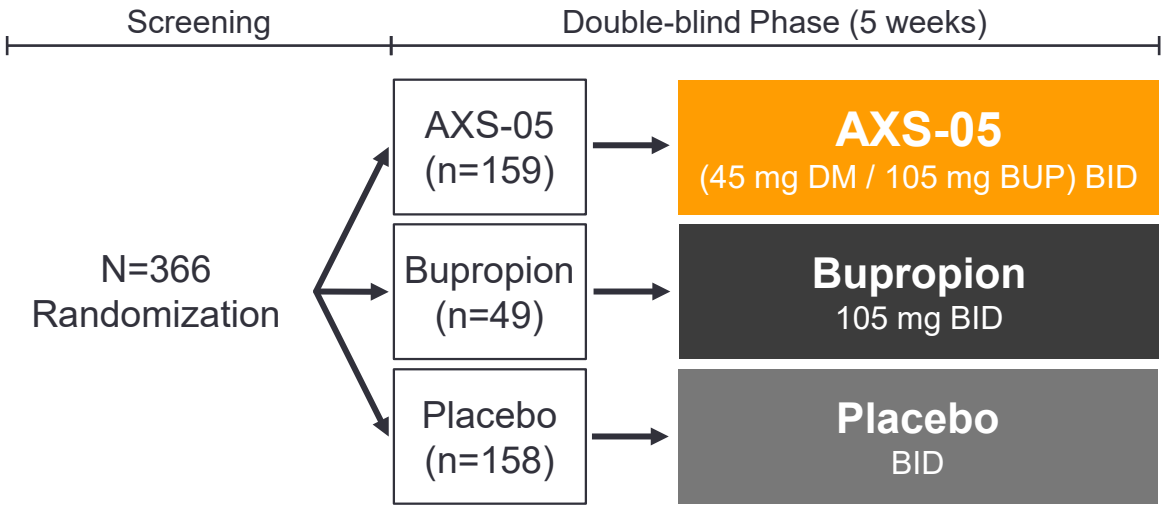
Cedric O'Gorman MD, MBA

Senior Vice President, Clinical Development and Medical Affairs
Axsome Therapeutics, Inc.

ADVANCE-1 Phase 2/3 Trial: Design Summary

ADVANCE STUDY

A Phase 2/3 trial to assess the efficacy and safety of AXS-05 in the treatment of Agitation in AD



BID = twice daily; BUP = Bupropion; DM = Dextromethorphan.

Dose titration:

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

Primary Endpoint:

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

ADVANCE-1 Phase 2/3 Trial: Key Entry Criteria

Inclusion criteria included:

- Male or female 65-90 years of age inclusive
- Diagnosis of probable Alzheimer's disease, according to the 2011 NIA-AA criteria
- Diagnosis of agitation, according to the IPA provisional definition of agitation
- MMSE between 10 and 24
- NPI-AA score ≥ 4
- Community-dwelling

Exclusion criteria included:

- Patient has dementia of non-Alzheimer's type
- Current use of SSRI/SNRI

Abbreviations: IPA = International Psychogeriatric Association; MMSE = Mini-mental state evaluation; NIA-AA = National Institute on Aging-Alzheimer Association; NPI-AA = Neuropsychiatric inventory – Agitation / Aggression domain; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

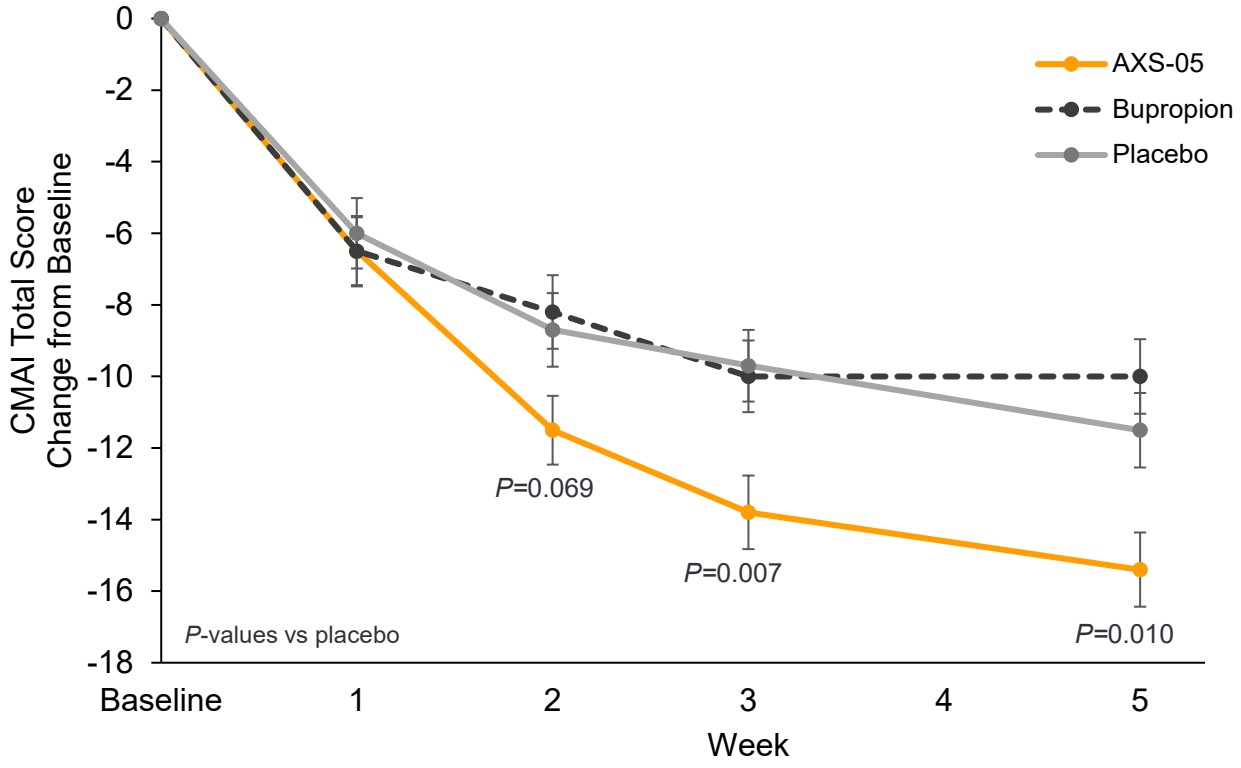
ADVANCE-1 Phase 2/3 Trial:
Demographics and Baseline Characteristics

	AXS-05 (n = 152)	Bupropion (n = 49)	Placebo (n=156)
Age (years)	75.2 (5.71)	76.4 (6.13)	75.1 (5.96)
Female Gender, n (%)	86 (56.6%)	22 (44.9%)	91 (58.3%)
Race, n (%)			
White	136 (89.5%)	43 (87.8%)	128 (82.1%)
Black or African American	11 (7.2%)	5 (10.2%)	25 (16.0%)
Asian	1 (0.7%)	0	1 (0.6%)
Other or Not Reported	4 (2.6%)	1 (2.0%)	2 (1.3%)
CMAI Score	60.7 (17.40)	66.1 (19.65)	59.4 (15.60)
CGI-S (agitation)	4.2 (0.77)	4.4 (0.82)	4.2 (0.65)
NPI-A/A Score	7.2 (2.17)	6.9 (2.45)	6.8 (2.07)
MMSE	18.7 (3.76)	17.8 (4.19)	18.8 (3.70)

mITT population. Data are mean (SD) unless otherwise stated.
Abbreviations: BMI = Body Mass Index; BUP = bupropion; CGI-S = Clinical Global Impression – Severity; CMAI = Cohen-Mansfield Agitation Inventory; DM = dextromethorphan; mITT = modified intent to treat; MMSE = Mini-mental state examination; NPI-A/A = Neuropsychiatric Inventory – Agitation and Aggression domain.

- Demographics and baseline characteristics were similar across all treatment groups
- Study completion rates were 86% across AXS-05 and placebo treatment groups

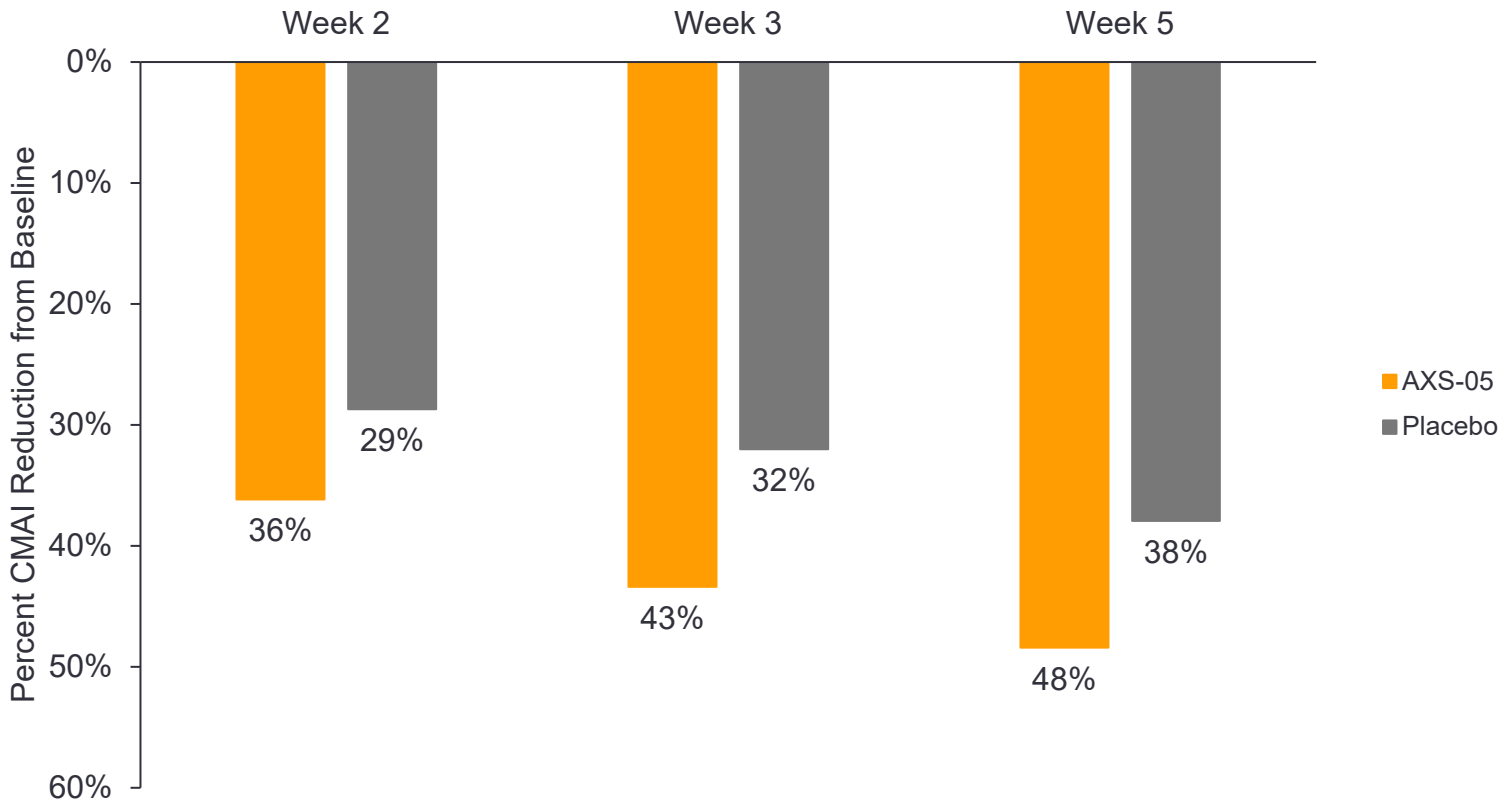
Improvement in Agitation Symptoms:
Change in Cohen-Mansfield Agitation Inventory (CMAI)



	AXS-05 (n = 152)	Bupropion (n = 49)	Placebo (n = 156)
Primary Endpoint: Change in CMAI total score at Week 5	-15.4	-10.0	-11.5
P-value vs. AXS-05		<0.001	0.010

Notes: P-values calculated from LSMean. Abbreviations: BID = twice daily; CMAI = Cohen-Mansfield Agitation Index

Clinically Meaningful Improvement:
Rapid and Substantial Reduction in Agitation



- Separation from placebo observed as early as Week 2

Notes: P-values calculated from LSMean.
Abbreviations: BID = twice daily; CMAI = Cohen-Mansfield Agitation Index

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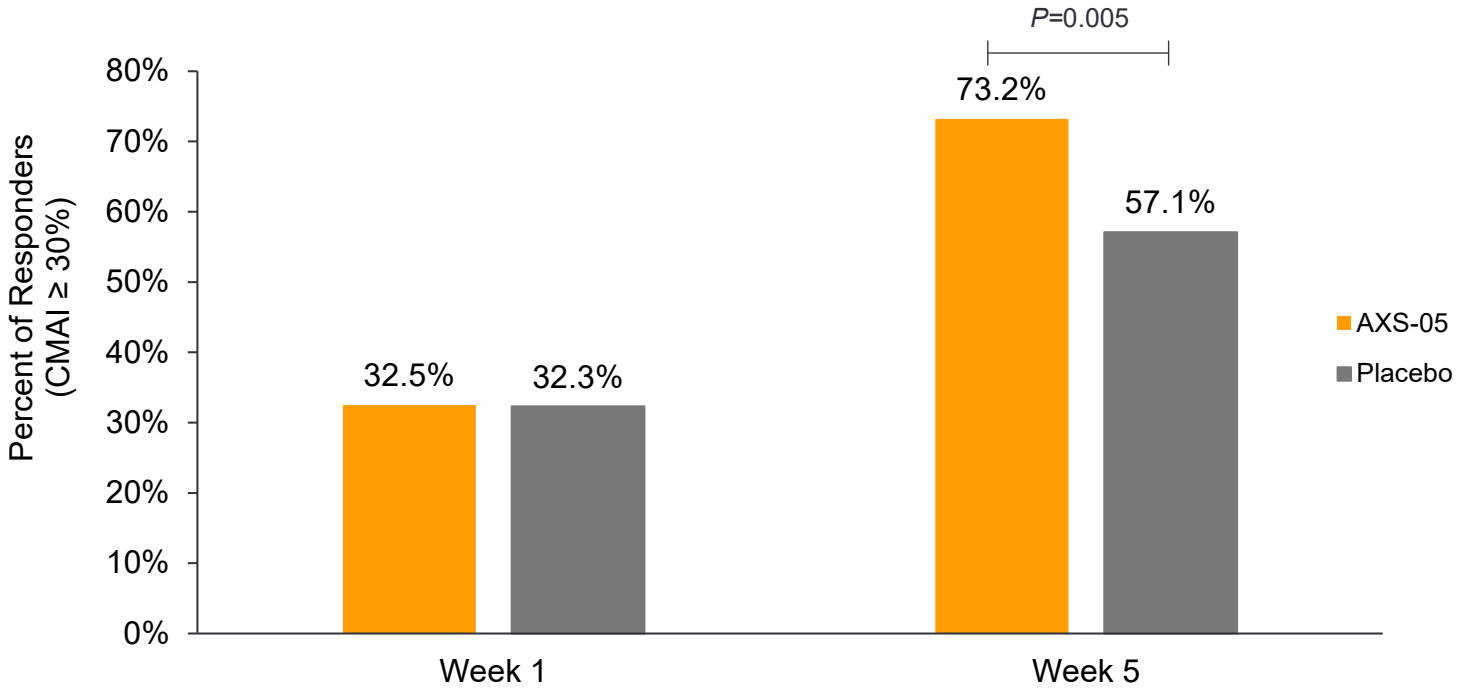
Clinical Response:
Reduction of ≥ 30% from Baseline in CMAI



- **mADCS-CGIC Agitation (clinicians' global assessment):** AXS-05 demonstrated superiority to placebo (p=0.036)

Notes: P-values calculated from LSMean.
Abbreviations: BID = twice daily; CMAI = Cohen-Mansfield Agitation Index; mADCS-CGIC = modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation

Safety Profile of AXS-05 in Alzheimer's Disease Agitation: Summary of Adverse Events

	AXS-05 (n = 159)	Bupropion (n = 49)	Placebo (n = 158)
Subjects with any TEAE	70 (44.0%)	30 (61.2%)	52 (32.9%)
Somnolence	13 (8.2%)	2 (4.1%)	5 (3.2%)
Dizziness	10 (6.3%)	5 (10.2%)	5 (3.2%)
Diarrhea	7 (4.4%)	3 (6.1%)	7 (4.4%)
Headache	6 (3.8%)	3 (6.1%)	4 (2.5%)
Falls	4 (2.5%)	7 (14.3%)	3 (1.9%)
Fatigue	3 (1.9%)	5 (10.2%)	2 (1.3%)
Insomnia	1 (0.6%)	3 (6.1%)	3 (1.9%)
Serious AEs	5 (3.1%)	4 (8.2%)	9 (5.7%)
Discontinuation due to AEs	2 (1.3%)	1 (2.0%)	2 (1.3%)
Deaths	0	1 (2.0%)	1 (0.6%)

Safety Population. Data presented as number of subjects (% of subjects). Treatment-emergent AEs occurring in ≥5% of subjects in any treatment group are presented.
Abbreviations: AE = adverse event; TEAE = Treatment-emergent adverse event.

- AXS-05 was not associated with cognitive impairment or sedation

ADVANCE-1 Phase 2/3 Trial Results: Summary

- AXS-05 met the primary endpoint in the ADVANCE-1 Phase 2/3 trial and rapidly, substantially, and significantly improved agitation in patients with Alzheimer's disease as compared to placebo
- AXS-05 was statistically significantly superior to bupropion, establishing component contribution
- AXS-05 resulted in a clinical response on the CMAI, defined as a 30% or greater improvement, in over 70% of patients, and was superior to placebo on clinicians' global assessment of agitation
- AXS-05 was generally safe, well tolerated
- AXS-05 was not associated with cognitive impairment or sedation

Q&A

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Concluding Remarks

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

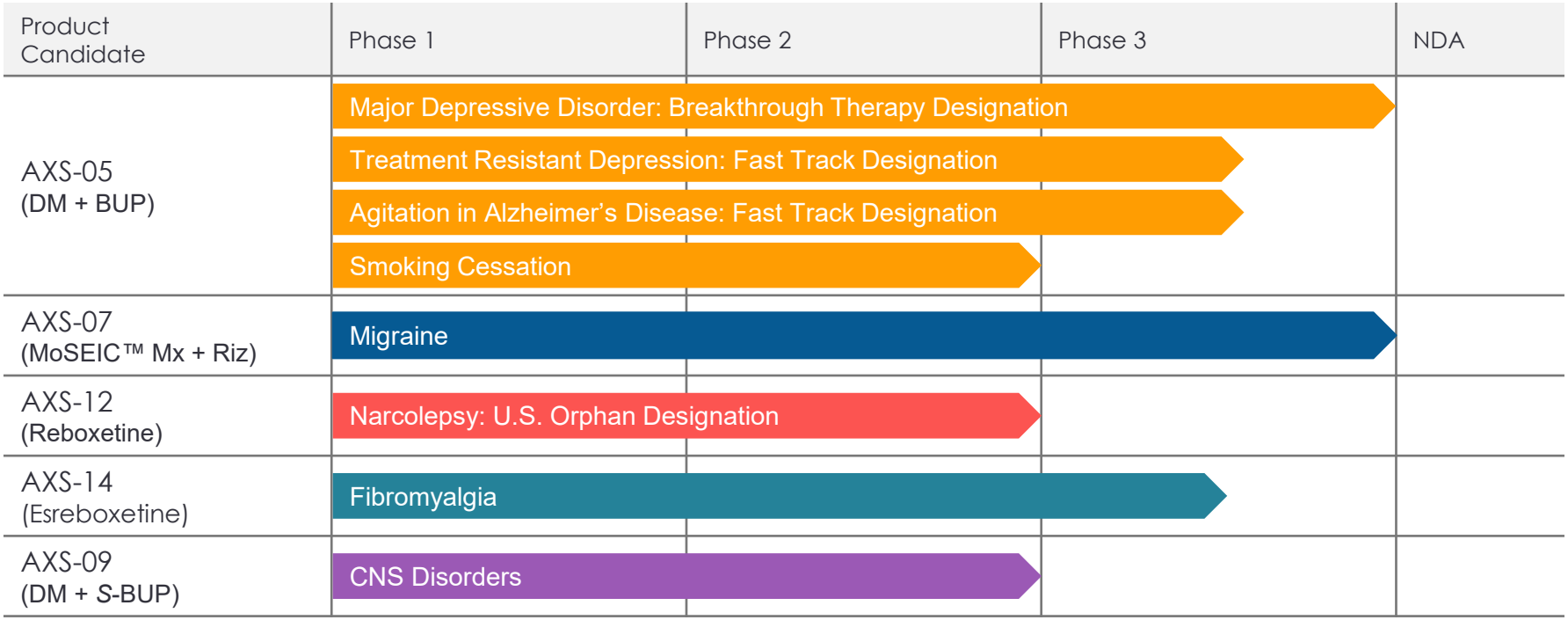
AXS-05:
Clinical Programs in Neuropsychiatry

	Clinical Program				
	ASCEND	**GEMINI**	**STRIDE-1**	**AXS-05 / OL**	**ADVANCE-1**
Indication	MDD	MDD	TRD	MDD/TRD	AD Agitation
Phase	Pivotal Phase 2	Pivotal Phase 3	Pivotal Phase 3	Open-label Phase 3	Pivotal Phase 2/3
Objectives	Efficacy of AXS-05 vs. BUP	Efficacy of AXS-05 vs. PBO	Efficacy of AXS-05 vs. BUP	Long-term safety of AXS-05	Efficacy of AXS-05 vs. BUP and PBO
Status	Completed	Completed	Completed	Ongoing	Completed
Subjects Dosed	96	326	310	876	366

Abbreviations: BUP = bupropion; MDD = Major Depressive Disorder; OL = Open-label; PBO = placebo; TRD = Treatment Resistant Depression

Our CNS Candidates and Pipeline

- Five differentiated clinical-stage CNS assets targeting significant and growing markets
- Patent protection to 2034-2036, worldwide rights for most product candidates



Abbreviations: BUP = Bupropion; CNS = Central Nervous System; DM = Dextromethorphan; Mx = Meloxicam; Riz = Rizatriptan; *S*-BUP = Esbupropion.

Our Clinical and Regulatory Milestones

Product Candidate	Indication	2020
AXS-05 (DM + BUP)	**MDD**	● **NDA** submission (4Q)
	TRD	✓ **STRIDE-1** Phase 3 topline results ● **Phase 3** trial start (3Q)
	AD Agitation	✓ **ADVANCE-1** Phase 2/3 topline results
	Smoking Cessation	● **FDA** meeting (2020)
AXS-07 (MoSEIC™ Mx + Riz)	**Migraine**	✓ **INTERCEPT** Phase 3 topline results ● **NDA** submission (4Q)
AXS-12 (Reboxetine)	**Narcolepsy**	● **Phase 3** trial start (2020)
AXS-14 (Esreboxetine)	**Fibromyalgia**	● **FDA** meeting (2020)

Abbreviations: AD = Alzheimer's Disease; BUP = Bupropion; DM = Dextromethorphan; MDD = Major Depressive Disorder; Mx = Meloxicam; Riz = Rizatriptan; TRD = Treatment Resistant Depression

✓ Accomplished milestone

● Upcoming milestone

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Thank you.

For more information, please contact

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