NASDAQ: AXSM

AXSOME THERAPEUTICS

AXS-05 Alzheimer's Disease Agitation

R&D Day

October 18, 2018

AXS-05 and Unmet Needs in Alzheimer's Disease Agitation

Introduction	**Mark Jacobson**, Senior Vice President, Operations
Axsome CNS Pipeline Overview	**Herriot Tabuteau, MD**, Chief Executive Officer
Prevalence and Consequences of Agitation in Alzheimer's Disease	**Jeffrey Cummings, MD, ScD**, Director Emeritus, Lou Ruvo Center for Brain Health, Cleveland Clinic
Pharmacological Management of Behavioral and Psychological Symptoms in People with Alzheimer's Disease	**Clive Ballard, MBChB, MRCPsych,** Pro-Vice-Chancellor, University of Exeter
AXS-05: A Potential New Treatment for Agitation in Alzheimer's Disease	**Jeffrey Cummings, MD, ScD**, Director Emeritus, Lou Ruvo Center for Brain Health, Cleveland Clinic
Panel Discussion and General Q&A	**Presenters** and **Cedric O'Gorman, MD**, Senior Vice President, Clinical Development and Medical Affairs and **Nick Pizzie,** Chief Financial Officer

Forward-Looking Statements & Safe Harbor

Certain information contained in this presentation may include “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials, interim analyses and receipt of interim results; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration or other regulatory authority approval of, or other action with respect to, our product candidates; the Company’s ability to obtain additional capital necessary to fund its operations; the Company’s ability to generate revenues in the future; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company’s research and development programs; the enforceability of the Company’s license agreements; the acceptance by the market of the Company’s product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. These factors could cause actual results and developments to be materially different from those expressed in or implied by such statements. Forward-looking statements are not guarantees of future performance, and actual results may differ materially from those projected. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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Axsome Therapeutics, Inc.
AXS-05 R&D Day
CNS Pipeline Overview

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

Our Technologies

Enabling new and innovative medicines to treat CNS conditions

Chiral & Formulation Chemistry

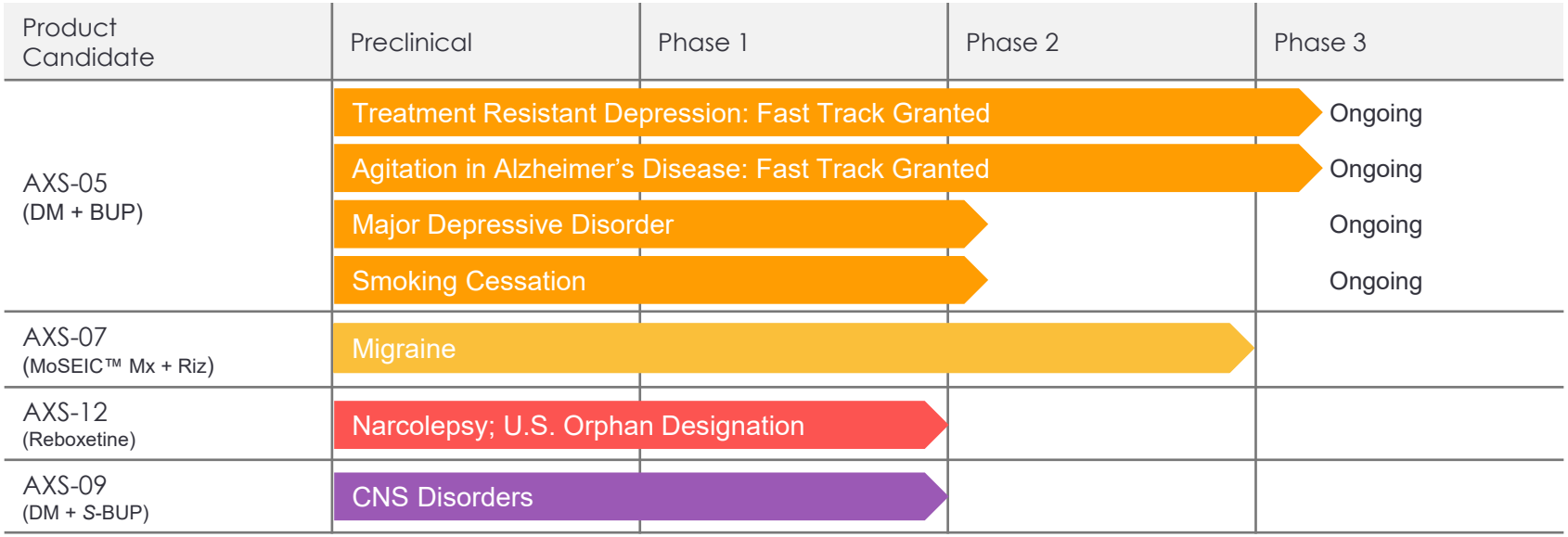
MoSEIC™ Delivery

Metabolic Inhibition

Chemical Synthesis & Analysis

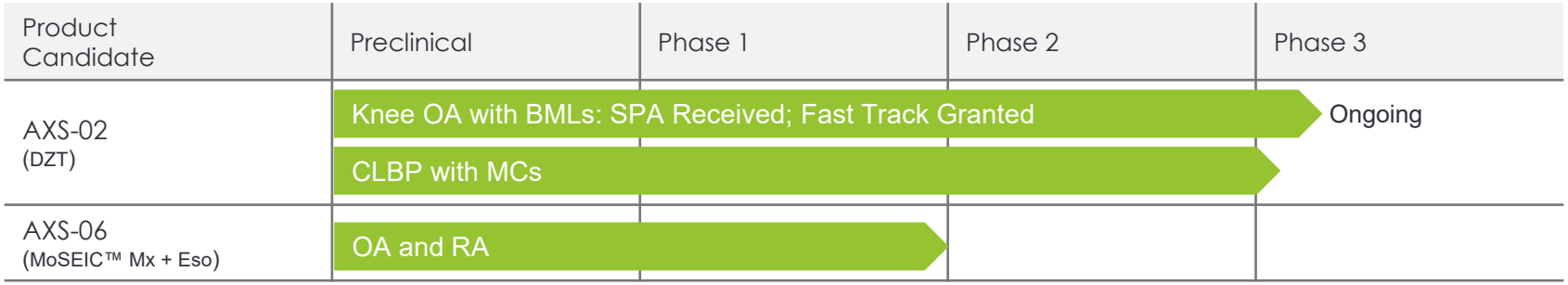
Our CNS Candidates and Pipeline

- Four differentiated clinical-stage CNS assets targeting significant and growing markets.
- Patent protection to 2034-2036, worldwide rights.



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

Axsome PPC Candidates and Pipeline



AXS-05:
Mechanisms of Action and Relevant Indications

Mechanism of Action	Pharmacodynamic Synergy: DM	BUP	AXS-05 DM+BUP	Relevant Indications[1]: ADHD	Anxiety	Alzheimer's	Depression	Fibromyalgia	OCD	Pain	Smoking cessation	Related Agents[2]
NMDA Receptor Antagonist	✓		✓			■	■			■		• Ketamine • Memantine (Namenda®)
Sigma-1R Agonist	✓		✓			■	■		■			• Fluvoxamine (Luvox®) • Donepezil (Aricept®)
Norepinephrine Reuptake Inhibitor	✓	✓	✓				■	■		■		• Duloxetine (Cymbalta®) • Venlafaxine (Effexor®)
Serotonin Reuptake Inhibitor	✓		✓		■		■		■			• Escitalopram (Lexapro®) • Fluoxetine (Prozac®) • Sertraline (Zoloft®)
Dopamine Reuptake Inhibitor		✓	✓	■			■				■	• Bupropion (Wellbutrin®)
Nicotinic ACh Receptor Antagonist	✓	✓	✓	■			■				■	• Bupropion (Wellbutrin®)

DM = Dextromethorphan; BUP = Bupropion. ✓ Present ■ Relevant

1. Indications listed are associated with the mechanism of action and are not related to either DM or BUP, unless specifically noted.
2. Agents do not contain DM or BUP, unless specifically noted.

AXS-05:
Treatment Resistant Depression

3M patients in the U.S.[1-3]

1% ≈ $150-300M*

- FDA Fast Track Designation
- Phase 3 ongoing
- Successful interim analysis for futility
  - IDMC recommended continuation; AXS-05 safe and well tolerated
- Interim analysis for efficacy anticipated 4Q 2018
- Full topline results 1H 2019

[1]Marcus SC, Olfson M. *Arch Gen Psychiatry* 2010;67:1265-1273.
[2]Rush AJ, et al. *Am J Psychiatry* 2006;163:1905-1917.
[3]U.S. Census Bureau, Population April 1, 2010 to July 1, 2013.

*Annual estimate for illustrative purposes.

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AXS-05:
Agitation in Alzheimer's Disease

2M patients in the U.S.[1,2]

1% ≈ $100-200M*

- FDA Fast Track Designation
- Phase 2/3 ongoing
- Interim analysis for futility anticipated 4Q 2018
- Interim analysis for efficacy anticipated 2019

[1]Ryu, SH, et al. *Am J Geriatr Psychiatry*. 2005;13:976-983.
[2]Hebert, LE, et al. *Neurology*. 2013;80:1778-1783.

*Annual estimate for illustrative purposes.

AXS-05:
Smoking Cessation

40M smokers in the U.S.
28M attempting to quit[1,2]

1% ≈ $1.3-2.7B*

- Phase 2 initiated in collaboration with Duke University
- Topline results expected 1Q 2019

[1]U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. 2014.
[2]Hughes JR, et al. *Addiction*. 2004;99(1):29-38.

*Annual estimate for illustrative purposes.

AXS-07:
MoSEIC™ Meloxicam + Rizatriptan for Migraine

15M Triptan U.S. Rx's written per year

1% ≈ $100M*

- Phase 3 initiation anticipated in 4Q 2018
- MoSEIC meloxicam delivers rapid, IV-like absorption with oral delivery, combined with 20-hour half-life.
- Potential for superior efficacy as compared to current treatments.

*Annual estimate for illustrative purposes.

AXS-12:
Narcolepsy

185,000 U.S. Patients

- AXS-12 (reboxetine) has potential to treat both cataplexy and excessive daytime sleepiness.
- Not expected to be scheduled (unlike all current approved narcolepsy medications).
- FDA Orphan Drug designation received
- Phase 2 initiation anticipated 4Q 2018, topline results in 1H 2019
- Only one drug (sodium oxybate) currently approved for cataplexy
  - Reported 2017 sales of sodium oxybate with only 13K patients treated: $1.19 Billion

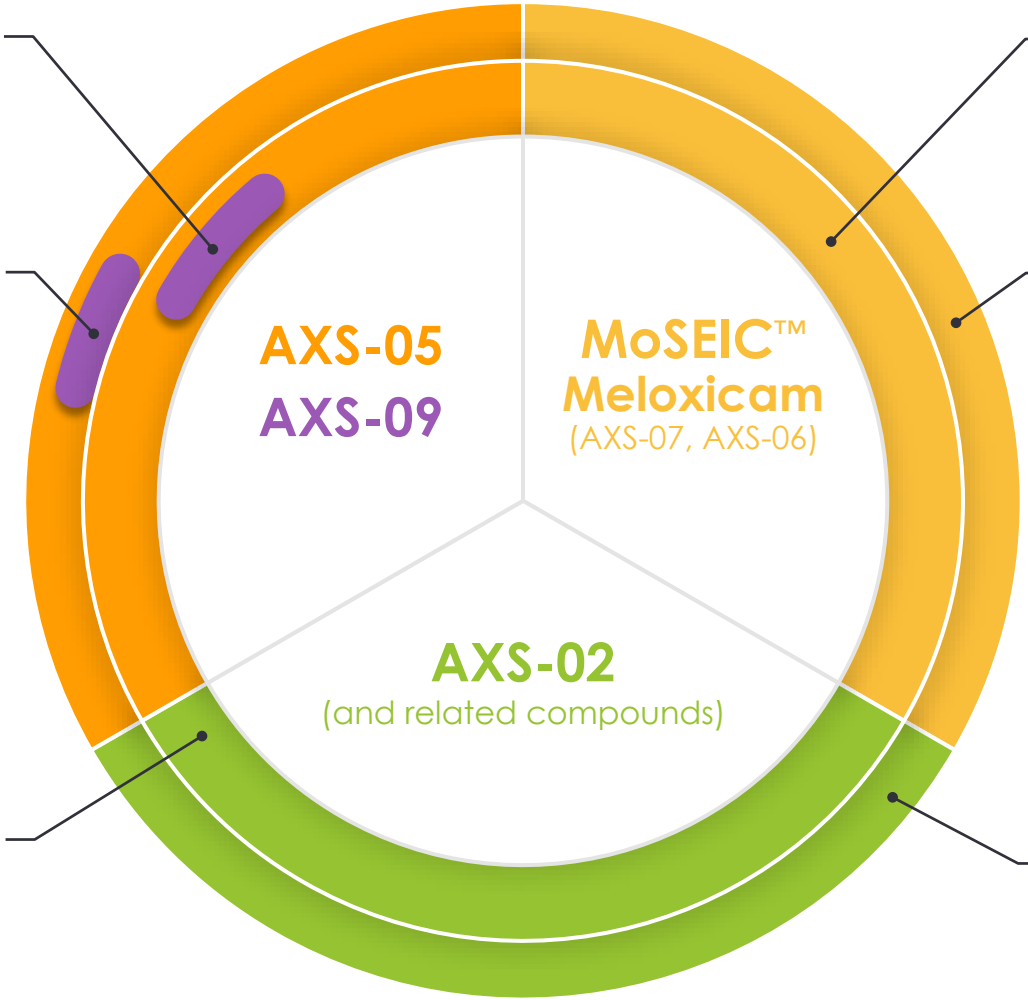
Broad Intellectual Property

29 Issued U.S. Patents
2 Issued O-U.S. Patents
Claims extending to **2034**
>45 pending

Proprietary Manufacturing
Drug Product Formulation

3 issued U.S. Patents
2 issued O-U.S. Patent
Claims extending to **2036**
>30 pending

Proprietary Manufacturing
Drug Product Formulation



91 Issued U.S. Patents
50 Issued O-U.S. Patents
Claims extending to **2034**
>65 pending

Proprietary Manufacturing
API Synthesis

Clinical Milestones

Product Candidate	Indication	2018	2019
AXS-05 (DM + BUP)	**TRD**	✓ **STRIDE-1** interim analysis ● **STRIDE-1** interim efficacy analysis (4Q 2018)	● **STRIDE-1** top-line results (1H 2019)
	AD Agitation	● **ADVANCE-1** interim analysis (4Q 2018)	● **ADVANCE-1** interim efficacy analysis ● **ADVANCE-1** top-line results (2H 2019/1H 2020)
	MDD	✓ **Ph 2** trial start ● **Ph 2** top-line results (4Q 2018)	
	Smoking Cessation	✓ **Ph 2** trial start	● **Ph 2** top-line results (1Q 2019)
AXS-07 (MoSEIC™ Mx + Riz)	**Migraine**	● **Ph 3** trial start (4Q 2018)	● **Ph 3** top-line results
AXS-12 (Reboxetine)	**Narcolepsy**	● **Ph 2** trial start (4Q 2018)	● **Ph 2** top-line results (1H 2019)

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.

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Prevalence and Consequences of Agitation in Alzheimer's Disease

Jeffrey Cummings, MD, ScD

Cleveland Clinic

Cleveland Clinic Lou Ruvo Center for Brain Health

Alzheimer's Disease and Behavioral and Neuropsychiatric Symptoms (NPS)

- Alzheimer's disease affects an estimated 5.3 million in the US and 50 million worldwide
- NPS is common, occurring in 80-90% of people with AD at some time in the course of their disease
  - Agitation (physical / verbal)
  - Psychosis
  - Depression
  - Apathy
  - Anxiety
  - Mania
  - Wandering
  - Excessive motor activity
  - Intrusiveness Resistance
  - Disinhibition
  - Sleep disturbances

Lyketsos CG, Carrillo MC, Ryan JM, et al., *Alzheimers Dement* 2011;7:532-539.

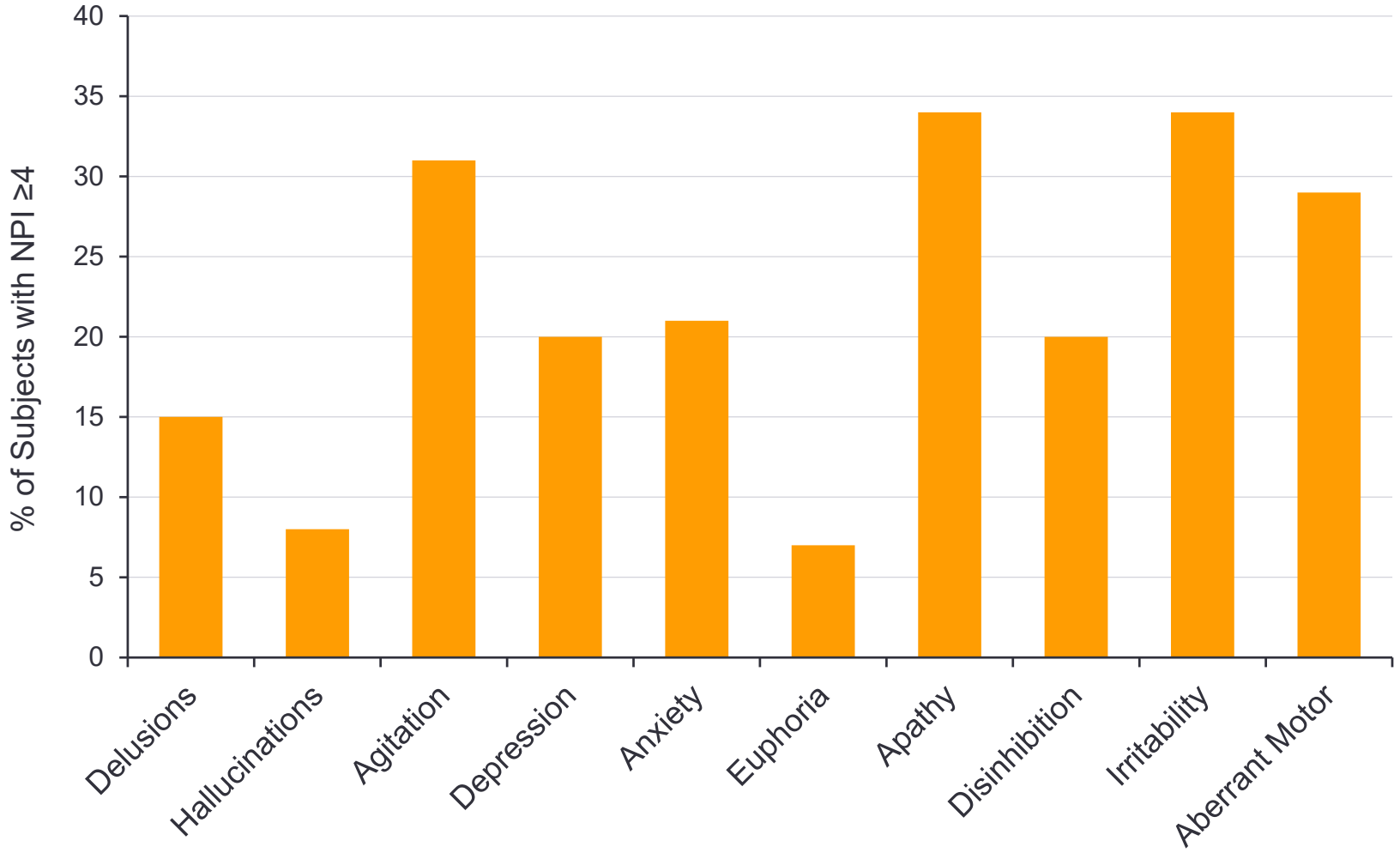
Defining Agitation

International Psychogeriatric Association (IPA) definition:

- Cognitive impairment syndrome
- 1 of the following associated with observed or inferred distress; persistent or recurrent x 2 weeks; change from premorbid behavior
  - Excessive motor activities
  - Verbal aggression
  - Physical aggression
- Severe enough to cause disability
- Comorbid conditions or environmental circumstances do not entirely account for the behavior

Cummings J, Mintzer J, Brodaty H, et al., Int Psychoger 2015;27(1):7-17.

Neuropsychiatric Symptoms in AD: Prevalence



Zuidema S et al. Internat J Geriatr Psychiatry 2007; 22: 632-838.
Dutch NH residents (N = 1322); mean GDS = 6

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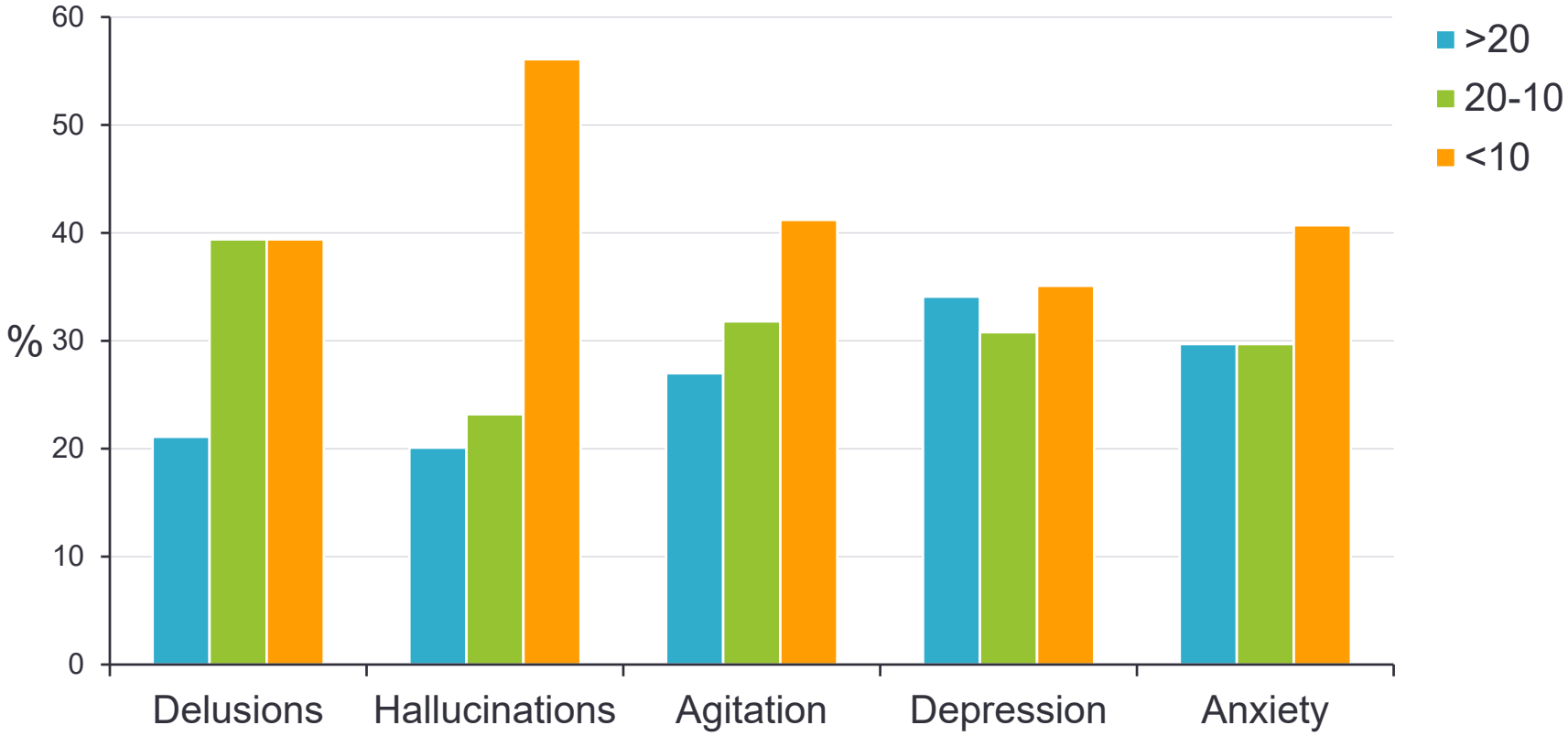
Neuropsychiatric Symptoms in AD: Disease Severity



MMSE Score (n)
>20 (n=119)
10-20 (n=125)
<10 (n=162)

Craig D, et al. *Am J Geriatric Psychiatry* 2005; 13: 460-468.

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Identifying NPS in Alzheimer's Disease: Neuropsychiatric Inventory (NPI)

- The Neuropsychiatric Inventory (NPI) assesses behavioral domains common in dementia:
  - Agitation/aggression, Dysphoria/depression, Apathy, Anxiety, Hallucinations, Delusions, Irritability, Disinhibition, Euphoria, Aberrant motor behavior, Sleep and Night-time Behavior Change, Appetite and Eating Change
- Each domain scored individually, with scores ≥ 4 representing presence of the symptom.

Identifying NPS in Alzheimer's Disease: Cohen-Mansfield Agitation Index (CMAI)

- Cohen-Mansfield Agitation Index (CMAI)
  - Defined agitation as inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the perceptible needs or confusion of the agitated individual.
  - CMAI as a scale to assess the frequency of a variety of agitated behaviors within the preceding two weeks in an individual.
  - There are three categories of agitated behaviors in the CMAI: verbally agitated, non-aggressive agitated behaviors, and aggressive behaviors.

Agitation and NPS: Consequences

- NPS are associated with decreased functioning, increased caregiver burden, earlier nursing home placement, accelerated progression to severe dementia, and increased risk of death.
- NPS are associated with a high risk of institutionalization.
  - Agitation (HR = 4.70)
  - Depression (Hazard rate = 3.06)
  - Delusions (HR = 5.74)
- NPS are associated with greater disability
  - 3 or more NPS → more disability
  - Depression → more basic activities of daily living impairment
  - Anxiety, appearance management behaviors → more instrumental activities of daily living impairment

Hongisto K et al. Int J Geriatr Psychiatry 2018; 33: 47-57.
Okura T et al. JAGS 2011; 59: 473-481.
Okura T et al. JAGS 2010; 58: 330-337

Agitation and NPS:
Cost

- Alzheimer's disease affects an estimated 5.3 million individuals in the United States and 50 million people worldwide, a number that is expected to double in 20 years.
  - Approximately 50% of patients have agitation.
- Annual societal costs of AD worldwide = $818 billion
  - 70% of the costs come from the US and Western Europe.
  - Recent prospective evaluation estimated agitation to account for 12% of health and social costs of AD
- 1-point worsening of the NPI score is associated with $247 - $409 per year in direct costs of care.

Alzheimer's Association, 2015;11(3):332-84.
Hurd et al., N Eng J Med 2013;368(14):1326-34.
Murman & Colenda, Pharmacoeconomics, 2005;23(3):227-42.
Morris S et al. Monetary costs of agitation in older adults with Alzheimer's disease in the UK: prospective cohort study. *BMJ Open*. 2015 Mar 13;5(3)

AXS-05 Pharmacology:
Relevance to AD Agitation and other NPS

Mechanism of Action	DM	BUP	AXS-05 DM+BUP
NMDA Receptor Antagonist	✓		✓
Sigma-1R Agonist	✓		✓
Norepinephrine Reuptake Inhibitor	✓	✓	✓
Serotonin Reuptake Inhibitor	✓		✓
Dopamine Reuptake Inhibitor		✓	✓
Nicotinic ACh Receptor Antagonist	✓	✓	✓

DM = Dextromethorphan; BUP = Bupropion. ✓ Present

AXS-05

- Fixed-dose combination of Dextromethorphan (DM) and Bupropion.
- Bupropion inhibits DM metabolism, and increases DM concentrations.

Clinical Evidence Suggests

- DM and Bupropion target neurotransmitter systems that are altered and that disrupt behavior in AD.

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Pharmacological Management of Behavioral and Psychological symptoms in People with Alzheimer's Disease

Clive Ballard, MBChB, MRCPsych

University of Exeter Medical School

Leiden Ranking 2018:
World Top 30 for Research Quality:

Drug Development for Alzheimer's Disease (AD): Historical Perspective

- Long period of time without new medicines for AD
  - No new symptomatic treatments since the cholinesterase inhibitors and memantine
  - No progress in therapies aimed at preventing the progression of AD
- Our understanding of the neurobiology of AD has developed but can it help us deliver clinical therapies that are effective?

Drug Development for Alzheimer's Disease (AD): Looking Forward

- Over 90% of people with AD experience neuropsychiatric symptoms (NPS)
  - Over 70% of people with AD experience agitation
  - Neuropsychiatric symptoms, especially agitation, are highly associated with adverse outcomes in AD
- Given the failures of disease-modifying drug development in AD, could NPS represent so-called "low hanging fruit" for researchers?

Agitation Associated with Alzheimer's Disease: Unmet Medical Need

- No approved treatments for agitation in AD
- Commonly used agents (off-label use)
- Antipsychotics:
  - Quetiapine
  - Risperidone
- SSRIs:
  - Citalopram
- Analgesics
- Benzodiazepines
- Anticonvulsants

Atypical Antipsychotics:
Risperidone Efficacy - BEHAVE-AD

	Target symptom	Mean difference from placebo	p value [95% CI]	95% CI
Risperidone 1mg	Psychosis	-0.79	p=0.03	-1.31 to -0.27
Risperidone 1mg	Aggression	-0.84	p=0.0002	-1.28 to -0.40
Risperidone 2mg	Aggression	-1.50	p<0.0001	-2.05 to -0.95

Ballard & Howard 2006 Nature Neuroscience Reviews.

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Atypical Antipsychotics:
Quetiapine Efficacy - STAR Trial

	Quetiapine 200mg (N=114)	Quetiapine 100mg (N=120)	Placebo (N=92)	Evaluation
PANSS-EC	-5.7 (0.9)	-4.9 (0.8)	-3.9 (0.9)	NS
NPI (total)	-9.7 (2.2)	-8.9 (2.1)	-8.2 (2.4)	NS
NPI (agitation)	**-1.1 (0.5)**	**-0.9 (0.5)**	**-1.2 (0.5)**	**NS**
NPI (psychosis)	**-2.5 (0.9)**	**-1.8 (0.8)**	**-2.5 (0.9)**	**NS**
CGIC	3.0 (0.2)	3.2 (0.2)	3.6 (0.2)	NS

PANSS-EC = Positive and Negative Syndrome Scale - Excitement Component; NPI = Neuropsychiatric Inventory; CGIC = Clinical Global Impression of Change; NS = Not significant

Zhong, et al Curr Alzheimer Res. 2007 Feb;4(1):81-93

Atypical Antipsychotics:

No Benefit and Accelerated Cognitive Decline with Quetiapine

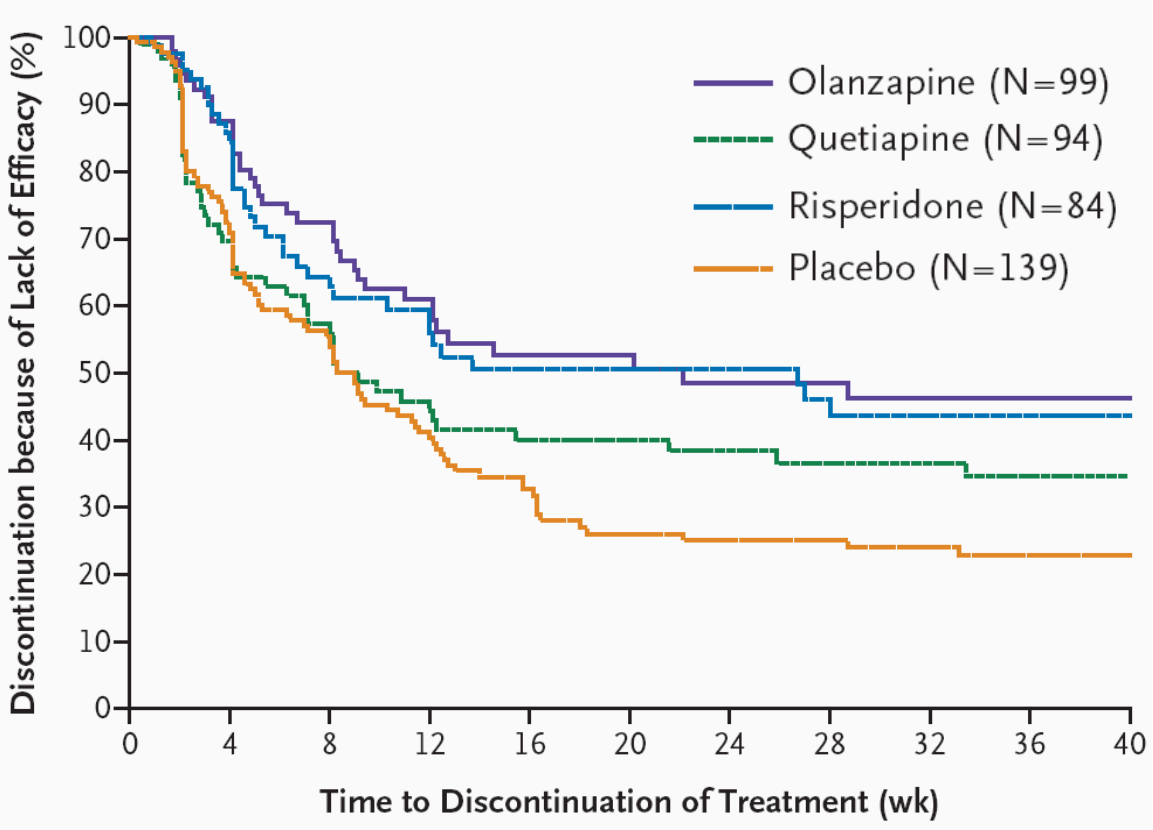
	Rivastigmine	Quetiapine	Placebo	Rivastigmine v PBO	Quetiapine v PBO
Week 6, mean (SD) change from baseline				**Mean difference (95% CI), p-val**	
CMAI	-5.1±16.3 (n=24)	-4.0±15.4 (n=27)	-6.2±17.6 (n=29)	4.1 (−4.2 to 12.3), P=0.3	3.5 (−3.7 to 10.8), P=0.3
SIB	+1.8±14.7 (n=14)	-10.5±14.8 (n=14)	+3.2±15.1 (n=18)	−3.5 (−13.1 to 6.2), P=0.5	−14.6 (−25.3 to −4.0), P=0.009
Week 26, mean (SD) change from baseline					
CMAI	-10.8±19.9 (n=24)	**-8.1±12.7 (n=27)**	**-9.0±16.5 (n=30)**	2.2 (−5.3 to 9.7), P=0.6	2.0 (−4.2 to 8.3), P=0.5
SIB	-3.1±20.6 (n=15)	**-11.3±15.6 (n=15)**	**+3.3±17.4 (n=19)**	−7.5 (−21.0 to 6.0), P=0.3	−15.4 (−27.0 to −3.8), P=0.01

CMAI = Cohen-Mansfield agitation inventory; PBO = placebo; SIB = severe impairment battery; SD = standard deviation

Ballard, et al. BMJ. 2005 Apr 16;330(7496):874.

Atypical Antipsychotics:
Declining Responses to Atypical Antipsychotics

- Response** based on CGIC score at 12 weeks:
  - 32% Olanzapine group
  - 26% Quetiapine group
  - 29% Risperidone group
  - 21% placebo group
- Overall comparison: p=0.22



*** A response was defined as continued treatment with the original phase 1 study drug and at least minimal improvement on the CGIC.*
Schneider L et al. *New England Journal of Medicine.* 2006; 355:1525-38.

Atypical Antipsychotics:
DART AD, Change from Baseline to 6 months

Assessment	Mean change (SD) Continue Treatment	Mean change (SD) Placebo	Estimated Mean Difference in Change (95% CI)	p-Value
Total NPI	(n=56) 1.3 (15.5)	(n=53) 4.5 (17.6)	-2.4 (-8.2 to 3.5)[3]	0.4
MUPDRS	(n=41) 0.8 (4.1)	(n=43) -0.4 (3.2)	1.3 (-0.4 to 3.0)[4]	0.1
Bristol ADL	(n=54) 1.8 (8.9)	(n=52) 0.2 (7.2)	1.7 (-1.2 to 4.6)[3]	0.2
Change in FAST[5]	(n=53)	(n=53)		0.9
-2	0	1		
-1	3	4		
0	34	32		
1	12	8		
2	4	8		
CGIC[5]	(n=48)	(n=48)		0.9
Very much improved	1 (2%)	0		
Much improved	3 (6%)	0		
Minimally Improved	7 (15%)	14 (29%)		
No Change	18 (37%)	14 (29%)		
Minimally worse	9 (19%)	10 (21%)		
Much worse	7 (15%)	10 (21%)		
Very much worse	3 (6%)	0		

Ballard et al PLOS Medicine 2008

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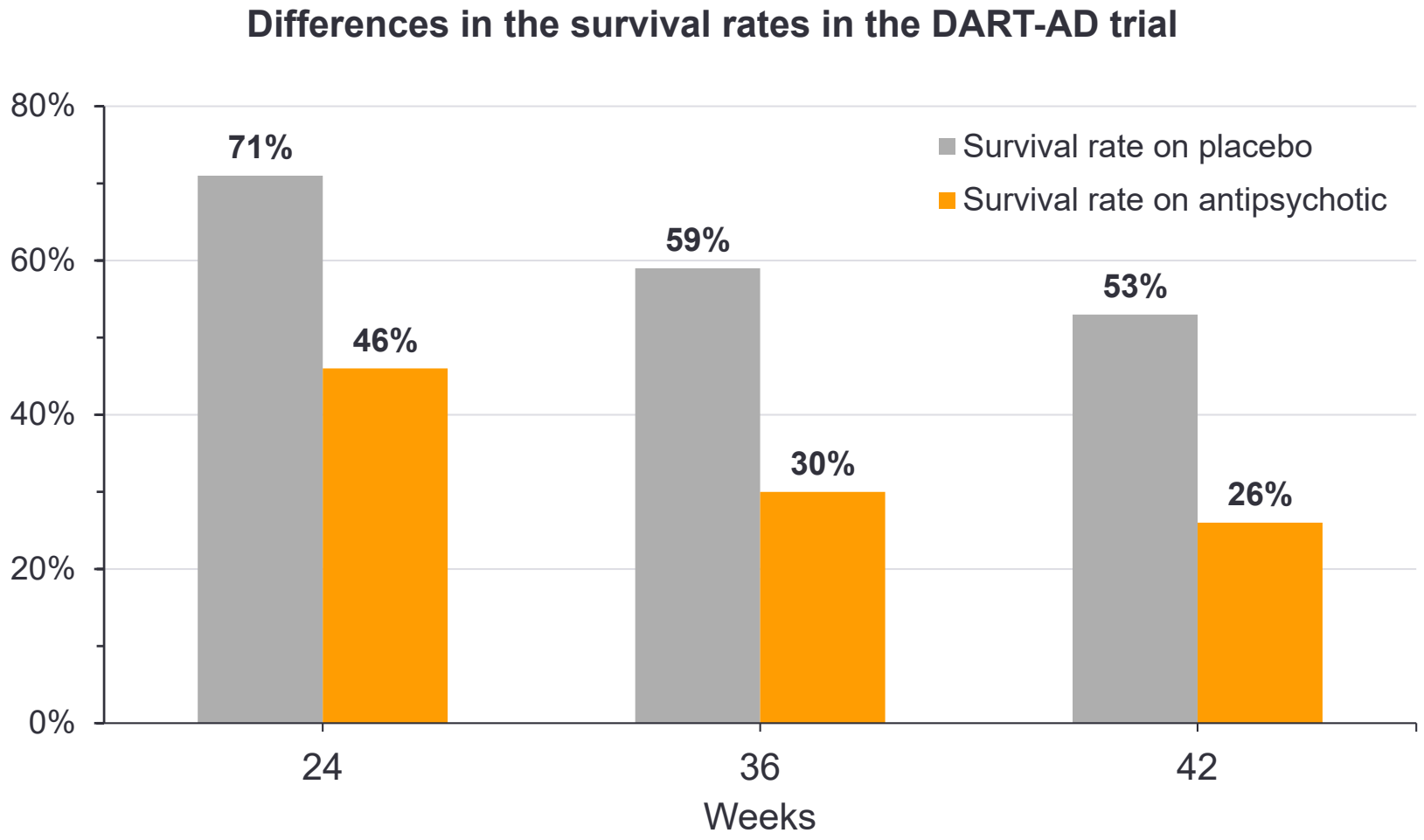
Atypical Antipsychotics: Limitations

- Mortality (1.5-1.7 fold)
  - Black box warning regarding use of antipsychotics in elderly patients with dementia
- Parkinsonism
- Sedation
- Gait disturbance
- Increased respiratory infections
- Edema
- Accelerated cognitive decline (2-4 fold)
- Stroke (>3 fold)
- Other thrombo-embolic events (up to 80%)

Schneider L et al. New England Journal of Medicine. 2006; 355:1525-38
Ballard, et al. Nat Rev Neurol. 2009 May;5(5):245-55..

Atypical Antipsychotics:
Declining Survival Rates



The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial.
Ballard, et al. Lancet Neurol. 2009 Feb;8(2):151-7

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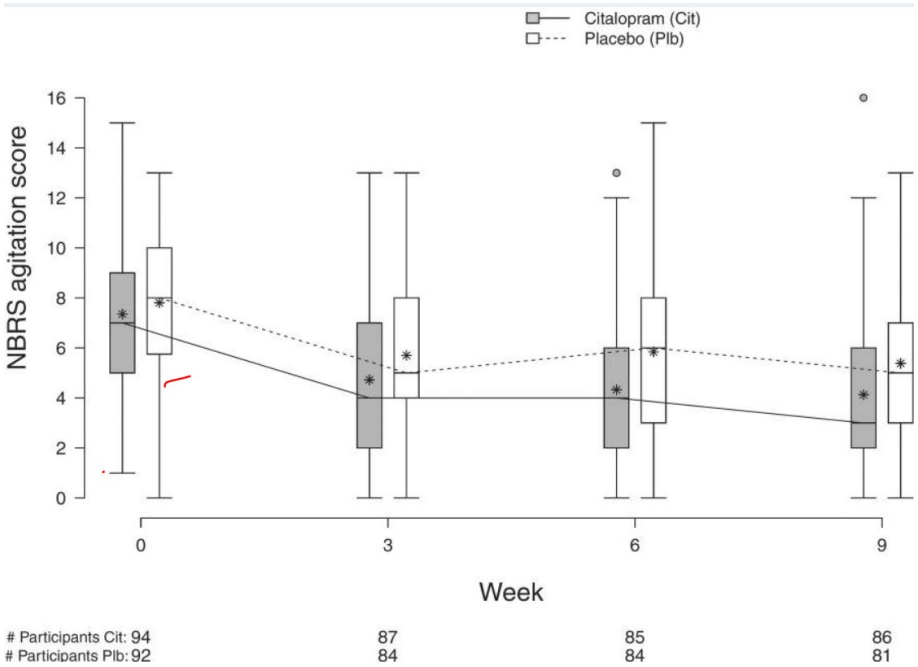
Citalopram: Citalopram for Agitation in AD(CitAD) - Design

- **Design, setting, and participants**:
  - Randomized, placebo-controlled, double-blind, parallel group trial with 186 patients with probable AD and clinically significant agitation
- **Interventions**:
  - 1:1 randomization to citalopram (n = 94) or placebo (n = 92) for 9 weeks
  - Doses titrated up to 30 mg per
- **Outcome measures:**
  - NBRS-A, mADCS-CGIC, NPI, CMAI

Porteinsson, et al. JAMA. 2014 Feb 19; 311(7): 682–691.

Citalopram:
Citalopram for Agitation in AD(CitAD) - Results



Endpoint	Treatment effect (95% CI)	P-val
NBRS-A	-0.93 (-1.80, -0.06)	0.04
mADCS-CGIC	2.13 (1.23, 3.69)	0.007
CMAI	-2.38 (-4.13, -0.63)	0.008
NPI-agitation	-0.78 (-1.77, 0.21)	0.12

Porteinsson, et al. JAMA. 2014 Feb 19; 311(7): 682–691.

Citalopram: Limitations in AD Agitation

- CitAD Trial Results
  - –Worsening of cognition (-1.05 points; 95% CI, -1.97 to -0.13; P = .03)
  - –QT interval prolongation (18.1 ms; 95% CI, 6.1-30.1; P = .01)
- Package insert for citalopram recommends maximum dose of 20 mg for elderly population, less than the 30 mg dose found to improve agitation symptoms in CitAD study

Non-Pharmacological Treatments (WHELD): Ballard et al PLOS Medicine 2018

Outcome measure	Adjusted effect (SE)*	p-Value	Mean difference (SEM)	95% CI of mean difference	Effect size (Cohen's D)	Number needed to treat$^{\Delta}$
DEMQOL-Proxy (n =553)	R = 0.12; Z = 2.82	0.0042	2.54^{+} (0.88)	0.81, 4.28	0.24	9
CMAI (n =553)	R = 0.11; Z = 2.68	0.0076	4.27^{+} (1.59)	−7.39, −1.15	0.23	6
NPI-NH (n=547)	R = −1.5; Z = 3.52	<0.001	4.55^{+} (1.28)	−7.07, −2.02	0.30	9

Effect estimates of WHELD intervention in comparison to TAU on primary outcome and key secondary outcome measures (multiple imputation analysis).
*Adjusted effect takes into account baseline value, age, sex, Clinical Dementia Rating, site, and clustering within care homes.

- The quality of interactions of positive care between care staff and residents with dementia (QUIS) was collected as a care-home-level assessment in 62 of the participating care homes. There was a statistically significant 19.7% greater increase in the proportion of positive care interactions from baseline to 9 months in the WHELD group compared to the TAU group (SEM 8.94; 95% CI 2.12, 37.16, p = 0.03; Cohen's D 0.55 AU:)

Pharmacological Treatments:
Husebo et al. BMJ, 2011

BMJ

RESEARCH

BMJ 2011;343:d4065 doi: 10.1136/bmj.d4065

Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial

Bettina S Husebo *postdoctoral fellow*[1], Clive Ballard *professor*[2], Reidun Sandvik *registered nurse*[1], Odd Bjarte Nilsen *statistician*[3], Dag Aarsland *professor*[4]

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Pharmacological Treatments:
Husebo et al. BMJ, 2011 - Results

Table 3| **Comparison of Cohen-Mansfield agitation inventory (CMAI) total score between control and intervention (stepwise protocol for treatment of pain) groups using repeated measures analysis of covariance (ANCOVA)***

Week	Mean (SD) CMAI total score		Effect of intervention on CMAI total†		Intracluster correlation coefficient‡
	Control group	Intervention group	Estimate (95% CI)	P value	
0	56.2 (16.1), n=177	56.5 (15.2), n=175	—	—	0.162
2	53.9 (17.0), n=161	52.0 (19.5), n=158	−3.6 (−0.5 to −6.7)	0.022	0.261
4	52.5 (16.3), n=160	49.4 (19.0), n=148	−4.1 (−0.9 to −7.4)	0.012	0.231
8	52.8 (16.8), n=157	46.9 (18.7), n=147	−7.0 (−3.7 to −10.3)	<0.001	0.226
12	52.5 (16.0), n=152	50.3 (20.3), n=142	−3.2 (0.1 to −6.4)	0.058	0.253

*Baseline score as covariate and least squares weighted by number of patients within cluster; P value from multivariate test of intervention was 0.002, and cross effect between week and intervention was <0.001.

†Variable estimate by week of effect of intervention on CMAI score from estimated model.

‡Proportion of total variance between clusters, and measured within framework of ANCOVA.

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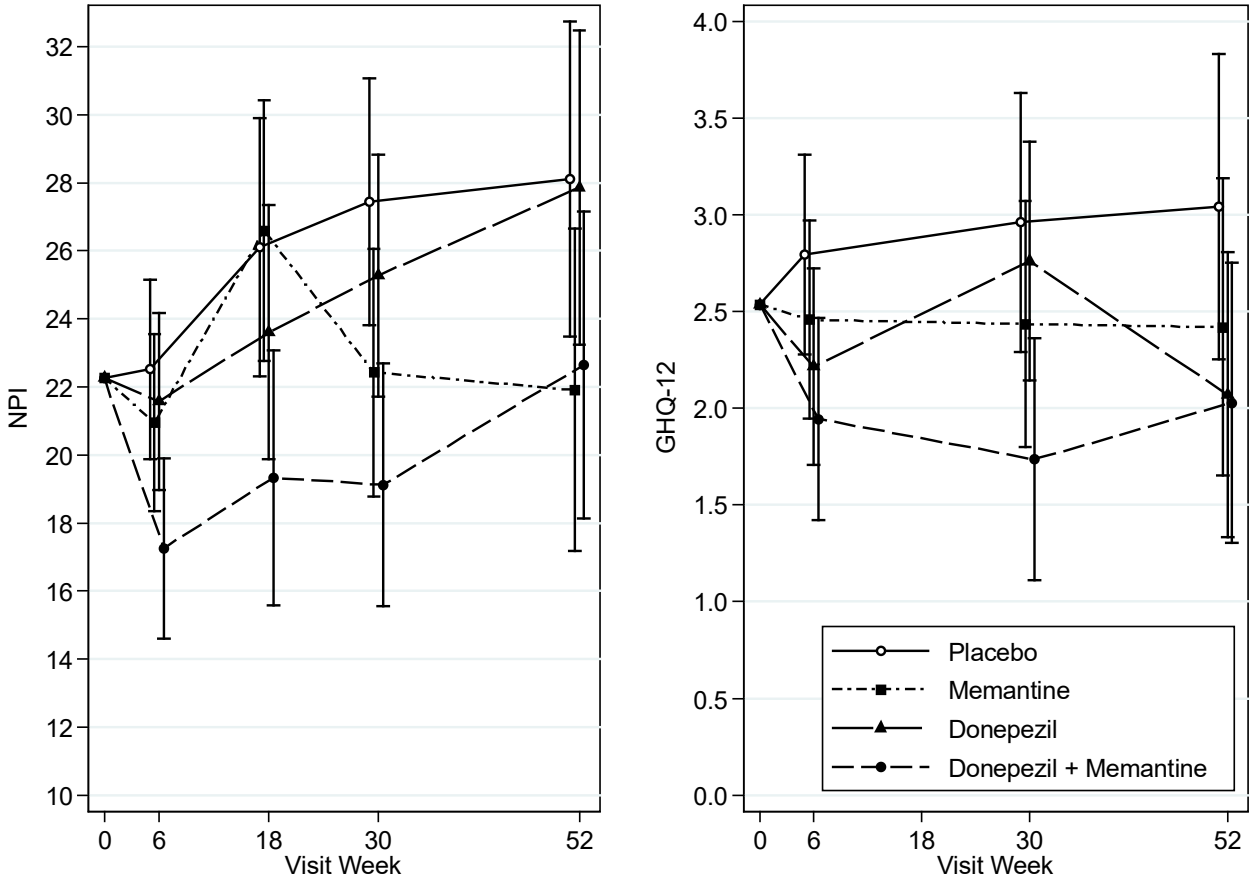
DOMINO: Estimates of Mean NPI and GHQ-12 by Visit and Treatment Arm



Howard et al. N Engl J Med. 2012 Mar 8;366(10):893-903.

FUTURE TREATMENTS

Atypical Antipsychotics:
Brexpiprazole

- Two 12-week RCTs of the atypical antipsychotic brexpiprazole in 700 participants with probable Alzheimer's disease and clinically significant agitation completed over the last year
- In one of the studies there was a significant benefit in agitation at the 2mg dose, but there were no benefits in global improvement compared to placebo
- In the second study, there were no significant benefits in agitation or secondary endpoints

http://www.lundbeck.com
Grossberg, et al. 40th Annual Meeting AAGP, March 15-18, 2018

Cost-effectiveness of Mirtazapine and Sertraline in Dementia: Randomised Controlled Trial

- Mirtazapine: Centrally active presynaptic α2-antagonist
- HTA SADD RCT (339 participants randomised and 326 with costs data (111 placebo, 107 sertraline, 108 mirtazapine). Taking the top 50% of raw NPI scores (ie those with appreciable BPSD):
  - There was a 7.1 point difference in NPI score (95%CI -0.50 to 14.68; p=0.067) between mirtazapine and placebo and a 13.2 point difference between mirtazapine and sertraline (95%CI 4.47 to 21.95; p=0.003).
  - From the cost effectiveness analyses, the time spent by unpaid carers caring for participants in the mirtazapine group was almost half that for patients in the placebo group (6.74 vs 12.27 hours per week) and sertraline group (6.74 vs 12.32 hours per week).
  - SYMBAD trial now ongoing in the UK

British Journal of Psychiatry, 202: 121-128.

Pimavanserin for AD Psychosis: Ballard et al 2018 Lancet Neurology

- 12 week RCT of people with AD in nursing homes with clinically significant psychosis (N=179)
- Primary outcome NPI psychosis at 6 weeks
- Key Secondary Outcome safety (cognition, function, parkinsonism, adverse events, mortality, agitation)
- Significant benefit in NPI psychosis at 6 weeks (Cohen's D 0.32) with good tolerability
- Benefits even more substantial in people with severe psychosis (NPI combined delusion and hallucination score ≥12) Cohen's D 0.73
- No benefit for agitation
- No increase of SAEs or mortality and no cognitive or functional decline compared to placebo

Effect of Dextromethorphan (DM) in AD Agitation: Clinical Experience Overview

- 220 patient randomized to dextromethorphan/quinidine (DM/Q) or placebo in 10 week trial
- Complicated 3:4 randomization design with re-randomization of placebo non-responders after 5 weeks
- 88% completed trial
- Significant benefits in agitation/aggression and CGIC, with benefits evident from week 1
- Falls and diarrhoea were the main emergent adverse events (both <10%)

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

AXS-05 (DM/Bupropion): Therapeutic Potential in AD Agitation

- When pharmacotherapy is required for AD agitation, options are severely limited.
- What degree of symptom severity can justify the use of atypical antipsychotics given their modest effect sizes and major adverse outcomes?
- Treatment with DM has been proposed due to the mechanistic antagonism of nicotinic α3β4 receptor, low-affinity N-methyl-D-aspartate, and inhibition of serotonin and norepinephrine reuptake.
- Change in NPI - agitation/aggression domain seen with DM (in presence of metabolic inhibitor) exceeds the commonly used threshold for clinical meaningfulness of 0.4 SDs
- Lack of adverse events, despite theoretical concerns regarding sedation, falls and mortality, suggests a great advantage over atypical antipsychotics

Corbett and Ballard. *Evidence Based Medicine*.2016 Feb;21(1):25.
Cummings JL et al., *JAMA* 2015;12(314):1242-54.

AXSOME
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Thank you.

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AXSOME THERAPEUTICS

AXS-05: A Potential New Treatment for Agitation in Alzheimer's Disease

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Cleveland Clinic

Cleveland Clinic Lou Ruvo Center for Brain Health

Disclosure:
Dr. Cummings is a consultant for Axsome Therapeutics

Agitation in AD:
Clinical Rationale for AXS-05

Neurotransmitter System	AXS-05 Pharmacologic Effect	Clinical Evidence
Glutamate	**NMDA Receptor Antagonism**	• Dysregulated in neuropsychiatric changes in AD • Memantine (NMDA receptor antagonist) reduced agitation vs. anticholinesterases[1] • Co-administration of DM and a metabolic inhibitor significantly reduced AD agitation[2]
Sigma-1	**Sigma-1 Receptor Agonism**	• Agents targeting sigma-1 have shown efficacy in behavioral disorders and AD • Lower density of sigma-1 receptors in AD patients vs. controls[3]
Serotonin	**Serotonin Reuptake Inhibition**	• Positive data with citalopram in patients with AD agitation[4]
Dopamine	**Dopamine Reuptake Inhibition**	• Bupropion inhibits DM metabolism leading to DM plasma concentrations associated with AD agitation reduction[2] • Bupropion relevance in treating other neuropsychiatric symptoms including depression and apathy[5]

1. Atri A, Agronin M, et al., Neurology. 2018;90(15):P6.175 | 2. Cummings J, et al. JAMA. 2015;314:1242-1254 | 3. Mishina, et al., Ann Nucl Med. 2008;2(22):151-6. | 4. Porsteinsson AP. et al. JAMA. 2014;311(7):682-691 |5. Corcoran C, Wong ML, O'Keane V. J Psychopharmacol. 2004;1(18):133-5

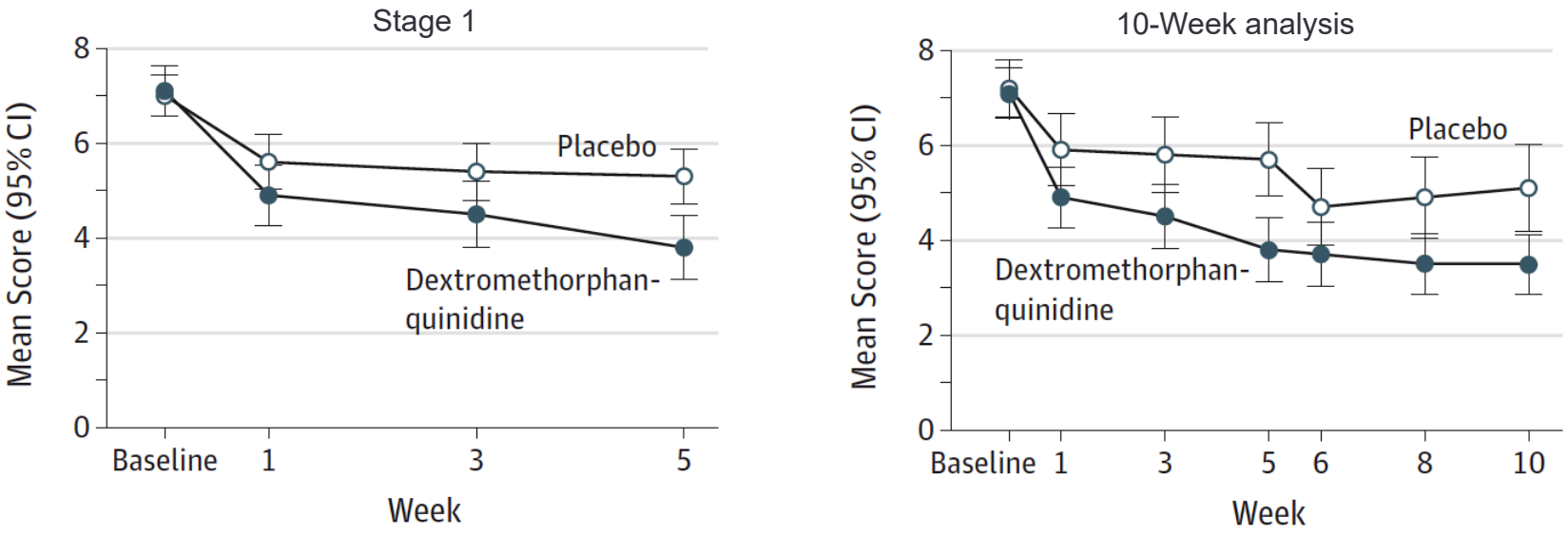
Dextromethorphan with Metabolic Inhibition: Trial in Agitation Associated with AD

- DM + quinidine (Q) studied in AD agitation
  - Quinidine, like bupropion, is a metabolic inhibitor that increases DM concentrations.
- Randomized, double-blind, placebo-controlled, two-stage trial:
  - Two consecutive 5-week stages
  - Placebo (n=125), 30 mg DM + 10 mg quinidine (Q) (n=93), for stage 1
- Enrolled patients with probable AD, CGI-S of 4 or more, MMSE 8 to 28
- Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.
- Primary endpoint: change on the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain – scale range, 0 (absence of symptoms) to 12 (symptoms occur daily and with marked severity).

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

Dextromethorphan with Metabolic Inhibition: DM + Inhibitor Reduces Agitation in AD

Mean Neuropsychiatric Inventory Agitation/Aggression Domain Scores



- 46% reduction in NPI Agitation/Aggression scores vs. 24% for placebo (P<0.001) at 5 weeks.
  - Results also significant for stage 2 and, at 10 weeks (P=0.002)
- Adverse events, DM+Q vs placebo: falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), and urinary tract infection (5.3% vs 3.9%).
- DM+Q was not associated with cognitive impairment or sedation.

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

Dextromethorphan with Metabolic Inhibition: Improvements in Secondary Measures

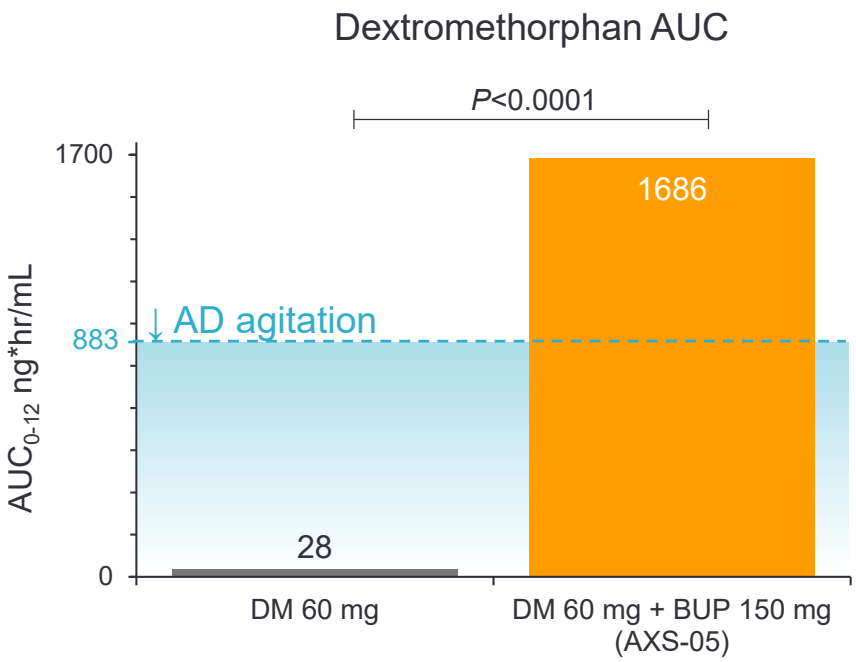
Table 2. Summary of Efficacy Outcome Measures in the Modified Intention-to-Treat Population

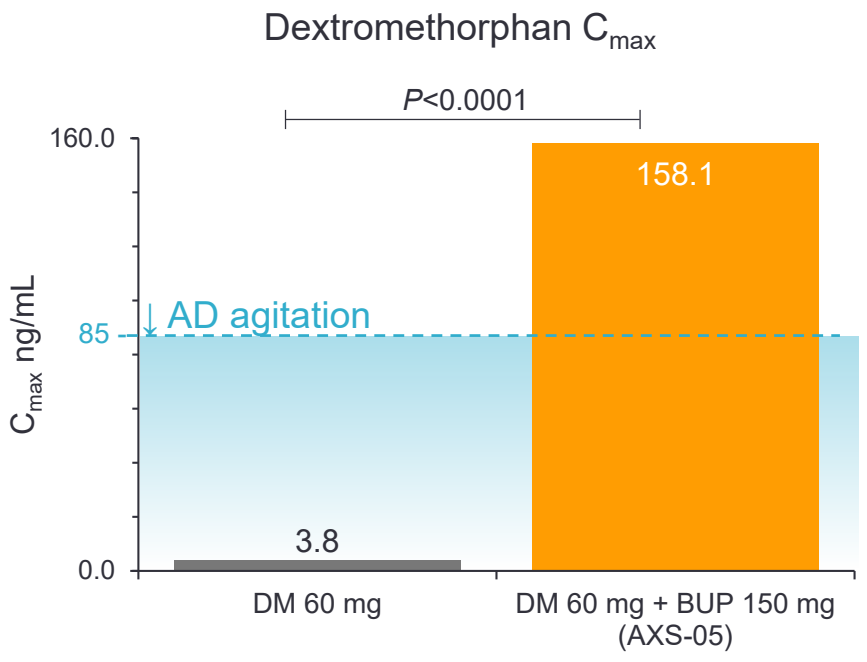
Outcome Measure and Study Stage[a]	No. of Participants		Change From Baseline, Mean (95% CI)		*P* Value by Stage[b]	Least Squares Mean Treatment Difference (95% CI)[c]	*P* Value by SPCD[b,d]
	Dextromethorphan-Quinidine	Placebo	Dextromethorphan-Quinidine	Placebo			
NPI Agitation/Aggression domain[e]							
Stage 1[a]	93	125	−3.3 (−3.9 to −2.6)	−1.7 (−2.3 to −1.2)	<.001	−1.5 (−2.3 to −0.7)	<.001
Stage 2[a]	44	45	−2.0 (−3.0 to −1.0)	−0.8 (−1.9 to 0.2)	.02	−1.6 (−2.9 to −0.3)	
10 wk[f]	93	66	−3.6 (−4.3 to −2.9)	−1.9 (−2.8 to −1.0)	.001	−1.8 (−2.8 to −0.7)	.003
NPI4A composite[e]							
Stage 1[a]	93	125	−7.3 (−9.1 to −5.4)	−4.5 (−6.0 to −3.0)	.03	−2.4 (−4.6 to −0.2)	.001
Stage 2[a]	44	45	−4.8 (−6.9 to −2.7)	−1.4 (−3.8 to 1.0)	.01	−3.9 (−7.0 to −0.9)	
10 wk[f]	93	66	−8.5 (−10.4 to −6.7)	−5.0 (−7.4 to −2.5)	.01	−3.4 (−6.1 to −0.7)	NA
NPI4D composite[e]							
Stage 1[a]	93	125	−7.6 (−9.4 to −5.7)	−4.0 (−5.5 to −2.6)	.006	−3.0 (−5.1 to −0.9)	<.001
Stage 2[a]	44	45	−4.6 (−6.8 to −2.4)	−1.9 (−4.2 to 0.4)	.02	−3.5 (−6.5 to −0.5)	
10 wk[f]	93	66	−8.3 (−10.1 to −6.5)	−5.0 (−7.4 to −2.6)	.02	−3.0 (−5.5 to −0.4)	NA
NPI Caregiver Distress agitation score[e]							
Stage 1[a]	93	125	−1.4 (−1.6 to −1.0)	−0.6 (−0.8 to −0.4)	<.001	−0.7 (−1.0 to −0.3)	.01
Stage 2[a]	44	45	−0.5 (−0.9 to −0.004)	−0.7 (−1.2 to −0.2)	.49	−0.2 (−0.8 to 0.4)	
10 wk[f]	93	66	NA	NA	NA	NA	NA
Cornell Scale for Depression in Dementia[g]							
Stage 1[a]	88	123	−1.0 (−1.8 to −0.3)	0.6 (−0.1 to 1.3)	.002	−1.6 (−2.5 to −0.6)	.02
Stage 2[a]	43	44	−0.9 (−1.8 to −0.004)	−0.7 (−1.5 to 0.1)	.75	−0.2 (−1.3 to 0.9)	
10 wk[f]	88	64	−1.2 (−2.0 to −0.4)	0.4 (−0.6 to 1.5)	.03	−1.3 (−2.6 to −0.1)	NA

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

AXS-05 Results in DM Concentrations Relevant for AD Agitation

DM Concentrations with AXS-05 and Therapeutic DM Levels for AD Agitation



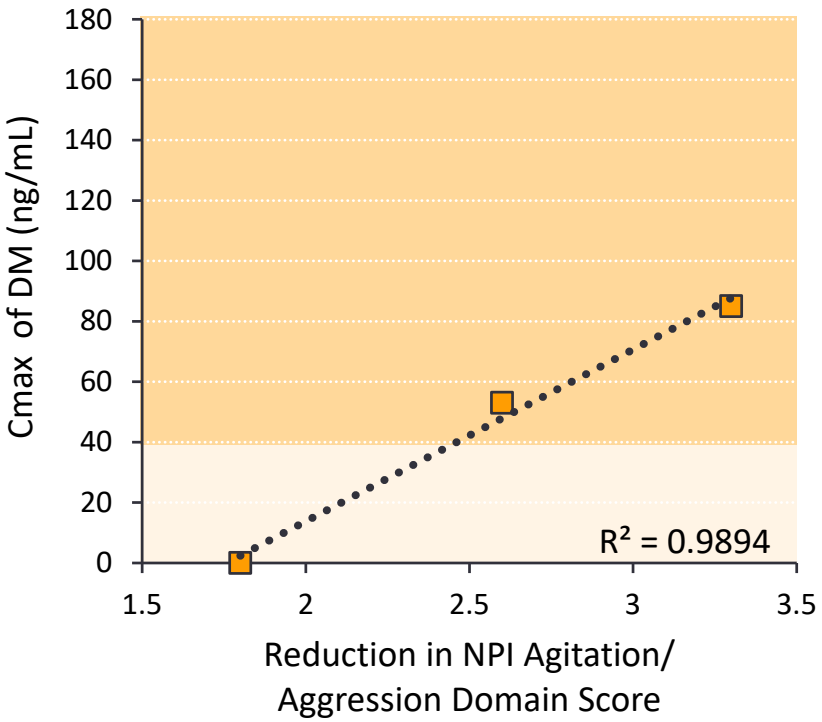


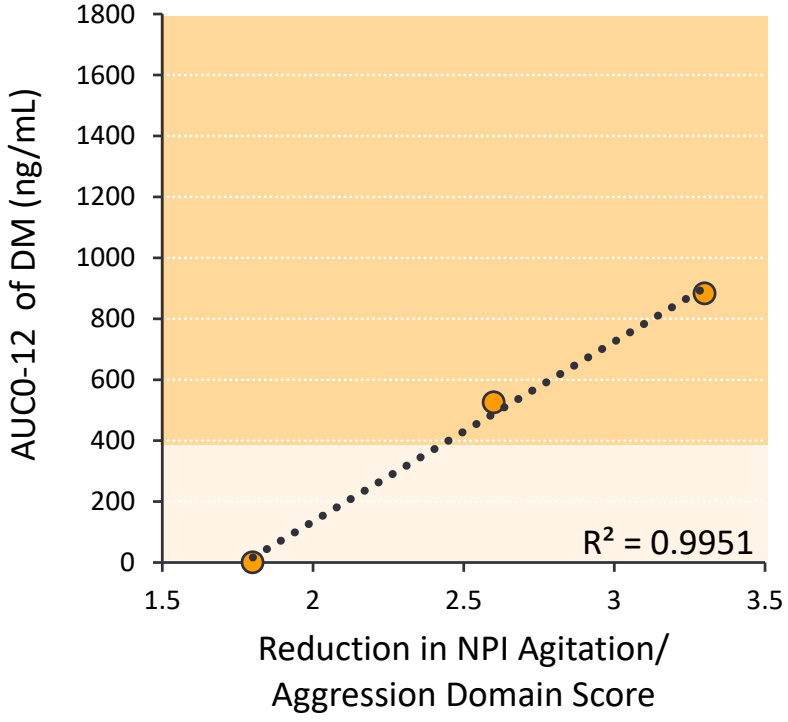
- AXS-05 data from Phase 1 pharmacokinetic trial.
- Dotted line shows DM plasma concentrations reported with dose (DM 30 mg + Q 10 mg) resulting in reduction of agitation symptoms in AD patients.

Axsome data on file.
Therapeutic DM concentrations from NDA 021879, FDA Clinical Pharmacology Review.
DM, Dextromethorphan; Q, Quinidine; BUP, Bupropion; AD, Alzheimer's disease; PBA, pseudobulbar affect

DM Concentrations with AXS-05: Correlation with Agitation Symptom Reduction

Reduction in Symptoms of Agitation as a Function of DM Plasma Levels





- Change in symptoms of agitation, reported in subjects with AD after co-administration of DM and the metabolic inhibitor quinidine, were plotted against the DM plasma concentrations associated with the doses used
- AUC and C_{max} ranges achieved with AXS-05 in the Phase 1 trial are shown by the shaded area

AXS-05 Pharmacology:
Bupropion May Target Other BPSDs in AD

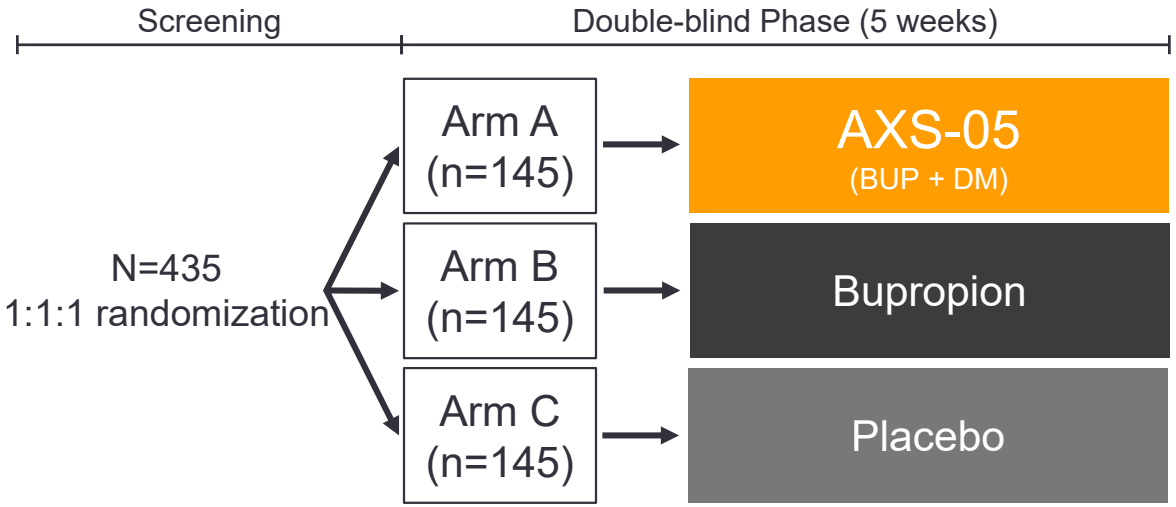
- Depression is the most common neuropsychiatric symptom in patients with AD with a reported 5-year period prevalence of 77%[1]
  - Bupropion is a well-established antidepressant.
- Apathy is another common neuropsychiatric symptom in patients with AD, with a reported 5-year period prevalence of 71%[1]
  - Case studies have indicated that bupropion may be efficacious in treating apathy.[2]
- Anxiety is a neuropsychiatric symptom reported in 62% of patients with AD over a 5-year period[1]
  - Several clinical studies suggest that bupropion is able to reduce anxiety[3]

[1]Steinberg H et al., *Int J Geriatr Psychiatry* 2008;2(23):170-7.
[2]Corcoran C, Wong ML, O'Keane V, *J Psychopharmacol* 2004;1(18):133-5; Marin RS et al., *J Neuropsychiatry Clin Neurosci* 1995;7(1):23-30.
[3]Bystritsky A et al., *Psychopharmacol Bull* 2008;1(41):46-51; Rush AJ et al., *Am J Psychiatry* 2006;11(163):1905-17.

Agitation in AD:
Phase 2/3 Design

ADVANCE STUDY

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



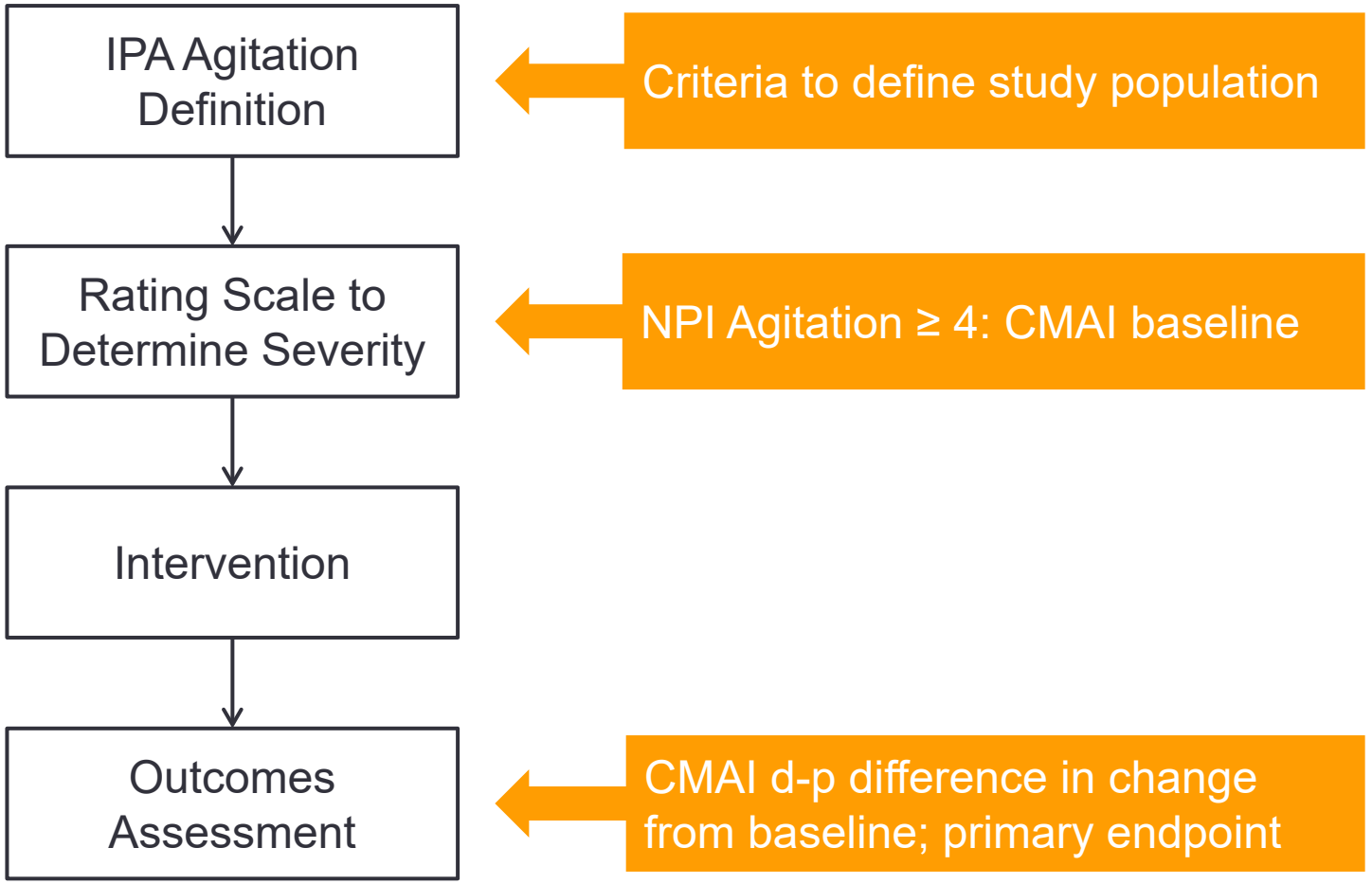
- **Primary Endpoint:** Cohen-Mansfield Agitation Inventory (CMAI)
- **Key Inclusion Criteria:**
  - Diagnosis of probable Alzheimer's disease
  - Clinically significant agitation
- Two interim analyses planned

Abbreviations: BUP = Bupropion; DM = Dextromethorphan.

Clinical Trials for Agitation AD: Progress Made

- Prior lack of consensus around definition of AD agitation resulted in variable trial results
- IPA definition of AD agitation brought about growing agreement, including with FDA
- No FDA-approved treatments to date despite continued prevalence of AD agitation
- Many treatments in development currently
- Growing importance amongst regulators regarding caregiver perspective in AD clinical trials
- Optimal clinical trial design must carefully define clinical condition, trial population and outcome measures

Clinical Trials for Agitation AD:
Trial Design



Abbreviations: CMAI = Cohen-Mansfield Agitation Inventory; NPI = Neuropsychiatric Inventory

Clinical Trials for Agitation AD:
Perspectives on Treatment Response

- Multiple perspectives, including caregivers, increase reliability of observed therapeutic response
  - Site rater // Caregiver // Patient
  - Caregiver perspective → caregiver rating
- NPI Distress scale provides an internal validity measure of the rating of the patient on the NPI

Conclusions

- The pharmacology of AXS-05 targets neurotransmitter systems believed to be altered in AD agitation.
- The DM component of AXS-05 has been shown reduce agitation when dosed with quinidine in a placebo-controlled trial.
- DM concentrations achieved with AXS-05 are in the range associated with a reduction in agitation measured using the NPI.
- The bupropion component of AXS-05, in addition augmenting DM concentrations, may be relevant to other neuropsychiatric symptoms in AD.
- A Phase 2/3 trial of AXS-05 in AD patients with agitation is ongoing.

Q&A

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Thank you.

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