Efficacy and Safety of AXS-05, a Novel Oral NMDA Receptor Antagonist with Multimodal Activity, in the Treatment of Alzheimer’s Disease Agitation: Results of the ADVANCE-1 Trial

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Presenter: Cedric O’Gorman, MD
Speaker Disclosures:

Cedric O’Gorman, MD is a full-time employee of Axsome Therapeutics Inc.
Alzheimer’s disease (AD) is the most common form of dementia and is characterized by cognitive decline and behavioral symptoms including agitation\textsuperscript{1,2}.

Agitation is seen in up to 70\% of AD patients\textsuperscript{2}:
- Emotional distress, aggressive behaviors, disruptive irritability, and disinhibition

Managing agitation is a major priority in AD\textsuperscript{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\textsuperscript{3}. 

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

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: 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.

• Neurotransmitter alterations in AD are thought to contribute to cognitive and behavioral symptoms including agitation and aggression.

• AXS-05 modulates the function of neurotransmitters (serotonin, glutamate, sigma-1, norepinephrine, and dopamine) implicated in AD.

Brain regions implicated in AD agitation

- AXS-05 pharmacological actions

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ADVANCE-1 Phase 2/3 Trial: Design Summary

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

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

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

N=366
Randomization

**Screening**

<table>
<thead>
<tr>
<th>AXS-05 (n=159)</th>
<th>Placebo (n=158)</th>
</tr>
</thead>
</table>

**Double-blind Phase (5 weeks)**

| AXS-05 (45 mg DM / 105 mg BUP) BID | Bupropion 105 mg BID | Placebo BID |

BID = twice daily; BUP = Bupropion; DM = Dextromethorphan.
### ADVANCE-1 Phase 2/3 Trial: Demographics and Baseline Characteristics

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

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)

Primary Endpoint: Change in CMAI total score at Week 5

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</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>-15.4</td>
<td>-10.0</td>
<td>-11.5</td>
</tr>
<tr>
<td>P-value vs. AXS-05</td>
<td>&lt;0.001</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

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
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

<table>
<thead>
<tr>
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<th>Placebo (n = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>70 (44.0%)</td>
<td>30 (61.2%)</td>
<td>52 (32.9%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (8.2%)</td>
<td>2 (4.1%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (6.3%)</td>
<td>5 (10.2%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (4.4%)</td>
<td>3 (6.1%)</td>
<td>7 (4.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (3.8%)</td>
<td>3 (6.1%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Falls</td>
<td>4 (2.5%)</td>
<td>7 (14.3%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.9%)</td>
<td>5 (10.2%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.6%)</td>
<td>3 (6.1%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5 (3.1%)</td>
<td>4 (8.2%)</td>
<td>9 (5.7%)</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>2 (1.3%)</td>
<td>1 (2.0%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>1 (2.0%)</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

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
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

• 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 at Week 5, establishing component contribution

• AXS-05 resulted in 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
Thank You
Q&A