Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder: Results of a Phase 2, Double-Blind, Active-Controlled Trial

ASCP 2019 Oral Session

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New Agents Needed for Treatment of MDD

- Major depressive disorder (MDD) is a disabling, chronic and prevalent condition. MDD is the leading cause of suicide in the U.S.²

- 63% and 44% of MDD patients have inadequate response to initial therapy and second line therapy, respectively.¹

- Current antidepressants are associated with a high rate of inadequate response (as much as 70%), and prolonged time to clinically meaningful response (up to 6-8 weeks).¹

- All currently approved oral MDD agents work primarily through monoaminergic mechanisms.³

Glutamatergic Signaling in MDD: Potential Role for NMDA Blockade

• Clinical and preclinical evidence has implicated dysfunctional glutamatergic neurotransmission in the pathophysiology of MDD, suggesting a role for NMDA receptor antagonism in the treatment of MDD.¹,²

• NMDA receptor blockade may result in improved antidepressant response and faster onset of action.¹,²

• Activation of AMPA receptors induced by NMDA receptor blockade induces downstream cascades involved in neural plasticity that may underlie antidepressant-like effects.³,⁴,⁵

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

• **NMDA receptor antagonism** – DM component of AXS-05
• **Sigma-1 receptor agonism** – DM component of AXS-05
• **Triple-reuptake inhibition** *(serotonin, norepinephrine, dopamine)* – DM and bupropion components of AXS-05
• **Modulation of DM plasma concentrations** – Bupropion component of AXS-05 increases DM concentrations into potentially therapeutic range.

• AXS-05 (dextromethorphan and bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.¹

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

Comparison of Receptor Binding and Activity for AXS-05 and Ketamine

<table>
<thead>
<tr>
<th></th>
<th>AXS-05 (DM + BUP)</th>
<th>Ketamine¹</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA receptor binding (IC₅₀)</td>
<td>402 nM</td>
<td>1047 nM</td>
<td>• Rat cerebellar granule neurons²</td>
</tr>
<tr>
<td>Sigma-1 agonist activity (Ki)</td>
<td>150 nM</td>
<td>140 μM</td>
<td>• Rat cerebellum³ or PC12 cells⁴</td>
</tr>
<tr>
<td>Serotonin reuptake inhibition (Ki)</td>
<td>23 nM</td>
<td>162 μM</td>
<td>• Rat brain synaptosomes⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Human kidney cells⁶</td>
</tr>
<tr>
<td>Norepinephrine reuptake inhibition (Ki)</td>
<td>240 nM</td>
<td>67 μM</td>
<td>• Rat brain synaptosomes⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Human kidney cells⁶</td>
</tr>
</tbody>
</table>

Analysis courtesy of Dr. Stephen M. Stahl


Abbreviations: BUP = Bupropion; DA = Dopamine; DM = Dextromethorphan; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate; SERT= Serotonin Reuptake Transporter; σ₁ = Sigma-1 Receptor
ASCEND Trial of AXS-05 in MDD: Design Summary

ASCEND (Assessing Clinical Episodes in Depression) Trial

Subjects with a confirmed diagnosis of moderate to severe MDD

- Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial
- Primary Endpoint: Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score over the 6-week treatment period (calculated at each time point and averaged)
- Extensive quality control measures

N = 80
1:1 randomization
N = 43
N = 37

Up to 4-week Screening Period

Double-blind Dosing Period (6 weeks)

AXS-05
(45 mg DM + 105 mg BUP)

Bupropion 105 mg

BUP = Bupropion; DM = Dextromethorphan
ASCEND Trial of AXS-05 in MDD: Key Entry Criteria

Inclusion criteria included:
- Male or female 18-65 years of age inclusive
- DSM-5 criteria for current MDD without psychotic features
- Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥ 25
- CGI-S score of ≥ 4 at baseline

Exclusion criteria included:
- History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current episode or in the past 6 months
- Schizophrenia, bipolar disorder, obsessive compulsive disorder
- Psychiatric symptoms secondary to any other general medical condition
## ASCEND Trial of AXS-05 in MDD:
Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AXS-05 (45 mg DM / 105 mg BUP) (n = 43)</th>
<th>Bupropion (105 mg) (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.3 (11.94)</td>
<td>37.7 (11.85)</td>
</tr>
<tr>
<td>Female Gender, n (%)</td>
<td>25 (58.1%)</td>
<td>26 (70.3%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>30 (69.8%)</td>
<td>20 (54.1%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>12 (27.9%)</td>
<td>14 (37.8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>≥ 3 Previous Depressive Episodes, n (%)</td>
<td>22 (51.2%)</td>
<td>19 (51.3%)</td>
</tr>
<tr>
<td>Baseline Clinical Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS Total Score</td>
<td>31.8 (4.04)</td>
<td>32.2 (4.46)</td>
</tr>
<tr>
<td>CGI-S Score</td>
<td>4.4 (0.50)</td>
<td>4.5 (0.51)</td>
</tr>
<tr>
<td>MADRS-6 Subscale Score</td>
<td>21.5 (2.42)</td>
<td>21.5 (2.97)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated.

BUP = bupropion; CGI-S = Clinical Global Impression – Severity; DM = dextromethorphan; MADRS = Montgomery-Åsberg Depression Rating Scale

- Demographics and baseline clinical characteristics were similar across both treatment groups.
- 23% of subjects had received prior first line treatment in their current major depressive episode.
- Study completion rates were >70% in both treatment groups.
Improvement in MADRS Total Score with AXS-05: Primary Endpoint

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>AXS-05</th>
<th>Bupropion</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in MADRS Total Score over 6-Week Period (averaged)</td>
<td>-13.7</td>
<td>-8.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in MADRS Total Score at Week 6</td>
<td>-17.2</td>
<td>-12.1</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Early and Sustained Remission with AXS-05: MADRS ≤ 10

Percent of Subjects Achieving Remission (MADRS ≤ 10)

<table>
<thead>
<tr>
<th>Week</th>
<th>AXS-05</th>
<th>Bupropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>26%</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>40%</td>
<td>16%</td>
</tr>
<tr>
<td>6</td>
<td>47%</td>
<td>16%</td>
</tr>
</tbody>
</table>

P-values:
- Week 1: P=0.184
- Week 2: P=0.004
- Week 3: P=0.005
- Week 4: P=0.022
- Week 6: P=0.004
Improvement in MADRS-6 with AXS-05: Core Symptoms of Depression

- The MADRS-6 is the sum of six of the 10 MADRS items that have been described as the core symptoms of depression.¹,²
- AXS-05 significantly improved the core symptoms of depression, as measured by the MADRS-6, versus bupropion, demonstrating a 12.58 point reduction in the MADRS-6 subscale compared to an 8.70 point reduction for bupropion at Week 6 (p=0.007).
- AXS-05 rapidly improved the core symptoms of depression as compared to bupropion, demonstrating numerical superiority as early as Week 1, and achieving statistical significance at Week 2 (p=0.027) and at every time point thereafter.

Rapid and Sustained Effect with AXS-05: Clinical Global Improvement

As early as Week 1, AXS-05 treatment resulted in a statistically significantly greater proportion of subjects who were much or very much improved, as measured by the CGI-I, as compared to bupropion (p=0.045).

The improvement over bupropion was maintained at Week 6 with 59% of patients treated with AXS-05 very much improved compared to 27% of those treated with bupropion (p=0.051).
Rapid and Sustained Effect with AXS-05: Clinical Response on MADRS-6 (≥ 50% improvement)

- As early as Week 1, AXS-05 resulted in a statistically significantly greater rate of clinical response on the MADRS-6 (≥ 50% improvement) as compared to bupropion (p=0.044).
- Statistical significance maintained at Week 6 (response rates of 63% for AXS-05 and 35% for bupropion, p=0.014).
• Remission may be defined by a MADRS total score of ≤ 12 (prespecified secondary endpoint).
• As early Week 1, 9% of patients treated with AXS-05 achieved remission versus no patients treated with bupropion (p=0.057).
• Rates of remission after 6 weeks of treatment were statistically significantly greater with AXS-05 than with bupropion (54% vs. 30%, p=0.032).
ASCEND Trial Results: Safety & Tolerability

• AXS-05 was safe and well tolerated in this trial with similar overall rates of adverse events being reported in both treatment arms.
• There were no reported serious adverse events.
• The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite and anxiety.
• The rate of discontinuations due to adverse events was approximately 12% for each treatment group.
• Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.
ASCEND Trial of AXS-05 in MDD: Conclusions

- AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, representing a potential mechanistically new approach for the treatment of depression.

- Treatment with AXS-05 in this trial resulted in rapid, substantial, and statistically significant improvement in depressive symptoms in patients with MDD.

- AXS-05 met the primary endpoint demonstrating statistically significant improvements on the MADRS total score versus the active comparator bupropion.

- Rapid antidepressant effects were seen as early as Week 1 (earliest assessment) and sustained through Week 6.

- Statistically significant effects for AXS-05 as compared to bupropion were observed on multiple secondary endpoints including MADRS-6, CGI-I, CGI-S, remission, and clinical response.

- AXS-05 was safe, well tolerated, and not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

- The novel mechanism of action of AXS-05 was associated with a differentiated clinical profile as compared to currently approved agents for MDD.