Rapid Reduction in Suicidal Ideation in Patients Treated with AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity: Results from the COMET-SI Trial

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Introduction
Major depressive disorder (MDD) is a chronic, disabling, prevalent, and life-threatening, biologically based disorder, and a leading cause of suicide.1 MDD is difficult to treat;2 63% of MDD patients experience an inadequate response to current first-line and second-line antidepressants in single-blind placebo trials, and the majority of these patients also fail second-line antidepressant therapy3-4. Need for mechanistically novel approaches: Currently approved oral antidepressants act primarily via monoaminergic mechanisms, and treatment associated with prolonged time to response (4 to 8 weeks) and adverse events that can impact adherence to treatment.5 Suicidal ideation is a major risk factor for suicide in patients with MDD;6-7 The timeline between the onset of suicidal ideation and suicide attempt is often short, highlighting the need for novel antisuicidal treatments.8 There is therefore an urgent need for:9-10
- Mechanistically novel, effective, well-tolerated, and rapidly-acting antidepressants that can provide sustained clinical benefit

Trial Objective
- The objective of the COMET-SI trial was to evaluate the efficacy and safety of an open-label AXS-05 treatment in MDD patients with suicidal ideation (SI)

Trial Design
- COMET-SI was a 2-arm (n=271 of the COMET-Clinical Outcomes with NMDA-based Depression Treatment) Phase 3, open-label trial (N=542) that evaluated the long-term efficacy and safety of AXS-05 for the reduction in suicidal ideation (SI) in MDD patients with suicidal ideation (SI) trial. The COMET-SI study enrolled 271 subjects completing a prior AX-S05 study and newly enrolled subjects. Subjects were treated with AXS-05 45 mg dextromethorphan-10 mg bupropion twice daily for up to 12 months. The AXS-05 SI trial evaluated those patients who had suicidal ideation, defined as a score of ≥3 on the Suicidality item of the Montgomery-Åsberg Depression Rating Scale (MADRS), at baseline.

Key inclusion criteria:
- Age 18 and older
- DSM-5 criteria for current MDD
- MADRS total score of ≥ 25
- MADRS score ≥ 3

Key exclusion criteria:
- History of ECT, vagus nerve stimulation, TMS, or experimental CNS treatment during the current episode or within 6 months
- Schizophrenic, bipolar disorder, obsessive compulsive disorder
- Psychological symptoms secondary to any general medical condition

Efficacy Outcome Measures:
- MADRS Score
- Resolution of Suicidal Ideation (SI) (n=1 on the MADRS score)
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Clinical Response (50% MADRS score reduction from baseline)
- Clinical Remission (SU score ≤1)
- Clinical Global Impression of Improvement (CGI)
- Sheehan Disability Scale (SDS) - Clinical Response in Functioning (SI score ≤ 12 on the SDS total score)

Baseline Demographics and Clinical Characteristics (COMET-SI)

<table>
<thead>
<tr>
<th>AXS-05 (n=271)</th>
<th>n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (range)</strong></td>
<td>57.7 (26.1-90.3)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>174 (64.1)</td>
<td>0.12</td>
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<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>167 (60.9)</td>
<td>0.02</td>
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<tr>
<td><strong>Black</strong></td>
<td>50 (18.5)</td>
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<tr>
<td><strong>Other/unknown</strong></td>
<td>54 (19.6)</td>
<td></td>
</tr>
<tr>
<td><strong>State (N=267)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>New York</strong></td>
<td>143 (53.1)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Massachusetts</strong></td>
<td>54 (20.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Other/unknown</strong></td>
<td>70 (26.3)</td>
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</tr>
<tr>
<td><strong>Baseline MADRS score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>58.9 (22.1)</td>
<td></td>
</tr>
<tr>
<td><strong>MADRS base/min (SI) score</strong></td>
<td>5.1 (4.1)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MADRS total/min (SI) score</strong></td>
<td>52.8 (15.0)</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>SI (n=271)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>12.9 (9.0)</td>
<td>0.01</td>
</tr>
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</table>

Efficacy Results
Reduction in Suicidal Ideation
- Treatment with AXS-05 was associated with an approximate 70% reduction from baseline in the MADRS score by Week 1, increasing to more than 80% by Week 4
- Resolution of suicidal ideation (MADRS ≤ 0.5) after treatment with AXS-05, was achieved by Week 1 in the majority of patients (78%), and in nearly all patients by Week 4

Improvement in MADRS Total Score
- Improvement in MADRS total score was observed with AXS-05 starting at Week 1, increasing to more than 80% by Week 4

Conclusions
- AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, representing a mechanistically novel approach for the treatment of MDD
- The COMET-SI satisfiedly evaluated the effect of open-label treatment with AXS-05 in reducing and resolving suicidal ideation, and improving depressive symptoms and functioning in MDD patients with suicidal ideation
- MDD patients with suicidal ideation, when treated with AXS-05, experienced rapid resolution of suicidal ideation, and improvement in overall depressive symptoms and functioning
- AXS-05 was generally safe and well-tolerated in this trial. The most commonly reported adverse events were dizziness, nausea, and headache

References
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9. MDD patients with suicidal ideation, when treated with AXS-05, experienced rapid resolution of suicidal ideation, and improvement in overall depressive symptoms and functioning
10. AXS-05 was generally safe and well-tolerated in this trial. The most commonly reported adverse events were dizziness, nausea, and headache

For more information, please contact Cedric O’Gorman at cogorman@axsome.com