Improvement in Anxiety Symptoms in Depressed Patients Treated with AXS-05 (Dextromethorphan-Bupropion): Results from the EVOLVE Open-label, Long-term Study

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Introduction

- Major depressive disorder (MDD) is a serious disorder.
- MDD is a chronic, disabling, prevalent, biologically-based disorder, and a leading cause of suicide.
- MDD is difficult to treat. In the largest open-label study conducted, STAR*D, only 1/3 of individuals with MDD achieved remission with up to 12 weeks of therapy with the SSRIs investigated.
- Anxiety in MDD: Anxiety has been reported in up to 50% of individuals with depression and has been associated with more difficult to treat depression.
- Second line treatment: In STAR*D, following non-remission with an SSRI, remission rates for second line treatments were 32% regardless of the exact treatment employed: switching to a different SSRI (citalopram), switching to an SNRI (venlafaxine), or switching to bupropion.
- Need for mechanistically novel approaches: The declining remission rates in STAR*D may be partially explained by the lack of pharmacological diversity among the different treatments.
- These actions modulate glutamatergic neurotransmission.
- Dysfunctional glutamatergic neurotransmission in the pathophysiology of MDD, suggesting a role for NMDA receptor antagonism in the treatment of MDD.
- There are emerging clinical data for new, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments.

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

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.
- The dextromethorphan component of AXS-05 is an agonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma 1 receptor agonist.
- The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a non-peptidic and dopamine reuptake inhibitor.

Objective

- To evaluate the effects of AXS-05 (15 mg dextromethorphan hyg•105 mg bupropion HCl) on anxiety in MDD patients who had been treated with at least 1 prior antidepressant in the current major depressive episode

Study Design: EVOLVE (Ixpost psychiatric Medication for Depression (Episodic)) is an open-label, US trial, in which patients were treated with AXS-05 twice daily for up to 15 months.
- Eligible patients were directly enrolled or had rolled in following completion of a prior AXS-05 study (MADRS), and had a DAS-D 5 diagnosis of MDD, a MADRS score of 21, and had been treated with at least 1 prior antidepressant in the current major depressive episode.
- A total of 186 patients were enrolled, consisting of 146 directly enrolled and 35 roll-in patients.
- Here we present the results for the directly enrolled patients.

Results

**Reduction in Hamilton Anxiety Rating Scale (HAM-A) Scores over Time**

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<tr>
<th>Month</th>
<th>AXS-05</th>
<th>HAM-A Scores over Time</th>
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</tr>
<tr>
<td>12</td>
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<td>20.0</td>
</tr>
</tbody>
</table>

**HAM-A Response (≥ 50% Improvement from Baseline)**

- 21.2% of patients achieved 50% improvement from baseline at Week 6.
- 27.9% of patients achieved 50% improvement from baseline at Week 12.
- Response on the HAM-A was achieved in 38.4%, 32.2%, and 27.9% of patients at Week 6, 12, and 24, respectively.
- Response rates continued to improve through Month 6 (73.7%) and Month 12 (77.3%).

Disclosures:
- Any Adverse Events
  - Advise against use in pediatric populations
  - Advise against use in pregnant and breastfeeding women
  - Advise against use in patients with known NMDA receptor antagonism

Conclusions

- Treatment with AXS-05 rapidly reduced anxiety symptoms in patients with MDD.
- Response and remission from anxiety symptoms were achieved as early as 1 week after starting treatment with AXS-05.
- Long-term treatment with AXS-05 was well tolerated.
- These data provide additional evidence for the efficacy of AXS-05 in MDD including those with prior treatment failures and those with anxious features.

References