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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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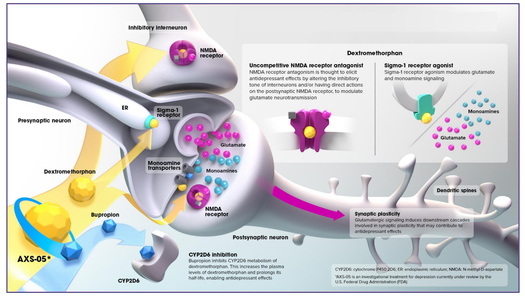
Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling, prevalent, biologically-based disorder, and a leading cause of suicide[1,2]
- **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 SSRI citalopram[3]
- **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[4]
- **Second line treatment**: In STAR*D, following non-remission with an SSRI, remission rates for second line treatments were ~ 25% regardless of the switch strategy employed: switching to a different SSRI (sertraline), switching to an SNRI (venlafaxine), or switching to bupropion[5]
- **Need for mechanistically novel approaches**: The declining remission rates in STAR*D may be partially explained by the lack of pharmacological diversity amongst the different treatments, e.g., all antidepressants employed are thought to work in generally the same way: monoamine modulation[6]
- **Glutamatergic hypothesis of MDD:** 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[1,7]
- **There is an urgent clinical need for:** New, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments[1]

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



AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:[1,5]

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist[8]
- These actions modulate glutamatergic neurotransmission
- The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor[8]

References

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5. Rush AJ, et al. N Engl J Med. 2006;354:1231-42..
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Objective

- To evaluate the effects of AXS-05 (45 mg dextromethorphan HBr-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

EVOLVE (Evaluation of NMDA Modulation for Depressive Episodes) was 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 (MERIT), and had a DSM-5 diagnosis of MDD, a MADRS score of ≥25, 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-over patients. Here we present the results for the directly enrolled patients

Efficacy Outcome Measures:

- Montgomery–Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HAM-A) scores
- Sheehan Disability Scale (SDS)

Statistical Analysis:

- Efficacy analyses were conducted on the mITT population which consisted of all patients who received at least 1 dose of AXS-05 and provided at least 1 post-baseline efficacy measurement
- Safety analyses were conducted on the safety population, which included all patients who received at least 1 dose of AXS-05
- Change from baseline P-values were analyzed using paired t-test

Key Inclusion / Exclusion Criteria	
Inclusion	**Exclusion**
▪ Male or female 18-65 years of age ▪ DSM-5 criteria for current MDD without psychotic features ▪ MADRS total score of ≥ 25 ▪ Treated with at least one prior antidepressant in the current major depressive episode	▪ History of seizure disorder, at risk of seizure, or any other condition that increases the risk of seizure ▪ Any current or recent medical, psychiatric, or social condition that was likely to interfere with the conduct of the study, confound the interpretation of study results, or endangers the patient's well-being

Demographics and Baseline Characteristics (mITT population)

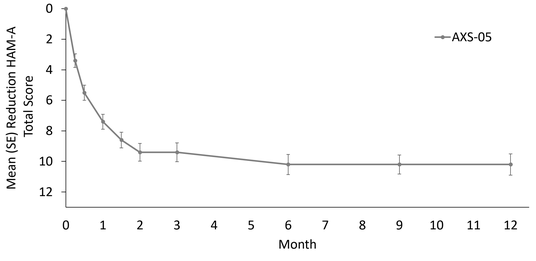
	AXS-05 (45 mg dextromethorphan – 105 mg bupropion) N=145
Demographics	
Age (years)	45.6 (13.07)
Female gender, n (%)	88 (60.7%)
Race, n (%)	
White	112 (77.2%)
Black or African American	25 (17.2%)
Asian	3 (2.1%)
Other	5 (3.5%)
Clinical Characteristics	
MADRS total score	32.2 (4.14)
CGI-S Score	4.5 (0.55)
HAM-A	15.6 (5.56)

Data are mean (SD) unless otherwise stated

- Baseline depression severity represents a moderate-to-severely depressed population
- Baseline anxiety severity represents mild-to-moderate anxiety

Results

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

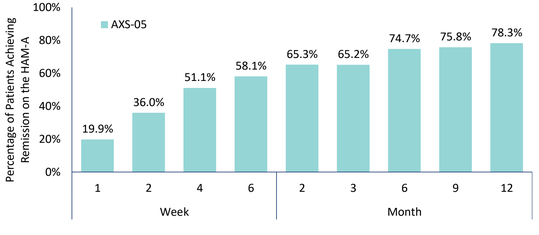


HAM-A Scores over Time

Week	Baseline	Week 1	Week 2	Week 4	Week 6	Month 2	Month 3	Month 6	Month 9	Month 12
HAM-A Score	15.6	12.3	10.0	8.0	6.8	6.1	5.9	5.2	5.0	4.6
P Value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

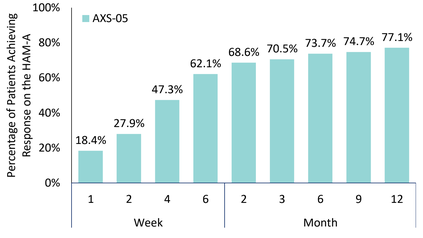
- Treatment with AXS-05 resulted in meaningful improvement in symptoms of anxiety
- Mean scores for HAM-A were < 7 at Week 6, indicating remission of anxiety symptoms
- Reductions from baseline to Weeks 1, 2, and 6 in the HAM-A were 3.4±5.34 (p<0.001), 5.5±5.81 (p<0.001), and 8.6±5.75 (p<0.001), respectively
- Improvements on the HAM-A were durable through Month 6 (-10.2±6.47; p<0.001) and Month 12 (-10.2±6.33; p<0.001)

HAM-A Remission (Score ≤ 7)



- Treatment with AXS-05 resulted in rapid rates of remission of anxiety
- By Week 4, over 50% of patients had achieved remission of anxiety symptoms
- Remission was durable, with 74.7% of patients remitting at Month 6 and 78.3% at Month 12

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



- Response on the HAM-A was achieved by 18.4%, 27.9%, and 62.1% of patients at Week 1, 2, and 6, respectively
- Response rates continued to improve through Month 6 (73.7%) and Month 12 (77.1%)

Safety and Tolerability

Adverse Events in ≥ 5% of Patients	AXS-05 (N=146)
Any Adverse Event	94 (64.4%)
COVID-19 infection	13 (8.9%)
Nausea	13 (8.9%)
Headache	11 (7.5%)
Dry mouth	9 (6.2%)
Dizziness	8 (5.5%)
Insomnia	8 (5.5%)

- Long-term treatment with AXS-05 was well tolerated
- COVID-19 infection, nausea, and headache were the most common AEs
- Discontinuation rate due to AEs was 8.9%
- Low rates of serious adverse events (5 patients; 3.4%) after long-term treatment with AXS-05. No SAE occurred in more than 1 patient.

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

We express our gratitude to the patients, investigators, and study staff for participation in this trial.