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Improvements in Cognitive and Physical Functioning Outcomes in Depressed Individuals Treated with AXS-05 (Dextromethorphan-Bupropion): Results from the EVOLVE Open-Label, Long-Term Study

Amanda Jones[1*], Maurizio Fava[2], Zachariah Thomas[1], Caroline Streicher[1], Shawn Alter[1], Herriot Tabuteau[1]

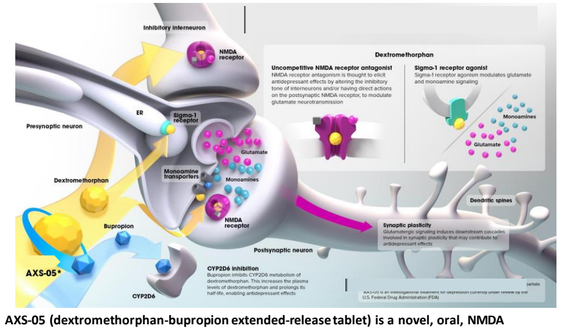
1. Axsome Therapeutics, New York, NY 2. Massachusetts General Hospital, Boston, MA

Axsome Therapeutics
1 World Trade Center, 22nd Floor
New York, NY 10007

Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling, prevalent, biologically-based disorder, and is 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]
- **Second line treatment**: In STAR*D, following non-remission with an SSRI, remission rates for second line treatments were ~ 20% regardless of the switch strategy employed: switching to a different SSRI (sertraline), switching to an SNRI (venlafaxine), or switching to bupropion[4]
- **Cognition and Physical Function:** Fatigue and cognitive dysfunction are common in MDD and are key symptoms that contribute to functional impairment[5-7]
- **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[8]
- **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[1,9]
- **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 (dextromethorphan-bupropion extended-release tablet) is a novel, oral, NMDA receptor antagonist with multimodal activity:[10-12]

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist
- 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
- AXS-05 (Auvelity®) was approved by the US FDA for the treatment of MDD in adults in August 2022

Objective

- To evaluate the effects of AXS-05 (45 mg dextromethorphan HBr-105mg bupropion HCl) 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 individuals with MDD were treated with AXS-05 (45 mg dextromethorphan HBr-105 mg bupropion HCl) twice daily for up to 15 months.

- Eligible individuals 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 181 individuals were enrolled, consisting of 146 directly enrolled and 35 roll-over; here we present the results for the directly enrolled individuals
- Newly enrolled individuals whose MADRS total score did not improve by at least 25% were discontinued from the study at Week 6
  - A total of 3 subjects met discontinuation criteria

Efficacy Outcome Measures:

- Montgomery–Åsberg Depression Rating Scale (MADRS), **MGH Cognitive & Physical Functioning Questionnaire (CPFQ),** 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
- Change from baseline was analyzed using paired t-test; P values were not adjusted for multiplicity

Cognitive & Physical Functioning Questionnaire[13]

The **CPFQ** is a 7-item patient-rated scale used to measure cognitive and executive dysfunction in mood and anxiety disorders. Each item is scored from 1-6, with higher scores indicating increasing impairment.

Domains Evaluated	Total Score Interpretation
Motivation/interest/ enthusiasm	≤ 7: Greater than normal functioning
Wakefulness/alertness	8-14: Normal functioning
Energy	15-21: Minimally diminished functioning
Focus/attention	22-28: Moderately diminished functioning
Ability to remember/recall information	29-35: Markedly diminished functioning
Ability to find words	36-42: Totally absent functioning
Sharpness/mental acuity	

Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
Male or female 18-65 years of age	History of seizure disorder, at risk of seizure, or any other condition that increases the risk of seizure
DSM-5 criteria for current MDD without psychotic features	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
MADRS total score of ≥ 25	
Treated with at least one prior antidepressant in the current major depressive episode	

Demographics and Baseline Characteristics (mITT population)

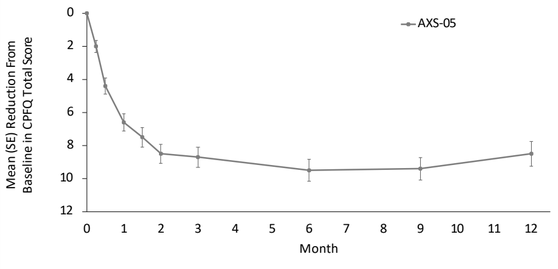
	AXS-05 (45 mg dextromethorphan – 105 mg bupropion) N=145
Demographics	
Age (years)	45.6 (13.07)
Female gender, n (%)	88 (60.7%)
Race, n (%)	
White	112 (77.2%)
Black or African American	25 (17.2%)
Asian	3 (2.1%)
Clinical Characteristics	
MADRS total score	32.2 (4.14)
CPFQ total score	28.4 (5.26)
HAM-A total score	15.6 (5.56)
SDS total score	17.5 (6.08)

Data are mean (SD) unless otherwise stated

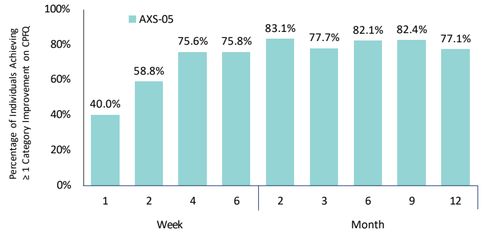
- Baseline depression severity represents a moderate-to-severely depressed population
- Baseline CPFQ scores indicate moderately to markedly diminished functioning
- Baseline anxiety severity represents mild-to-moderate anxiety

Results

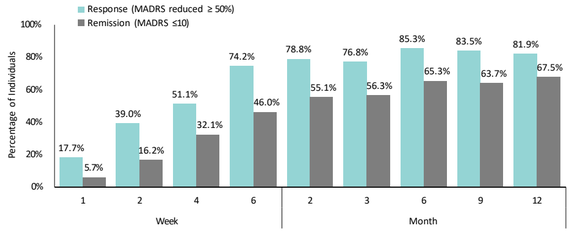
Improvement in Cognitive & Physical Functioning Questionnaire



Categorical Improvement in the CPFQ



Clinical Response & Remission with AXS-05



Rapid and Durable Improvements with AXS-05 Across Multiple Measures

	Week 1	Week 2	Week 4	Week 6	Month 2	Month 3	Month 6	Month 9	Month 12
Mean Improvement from Baseline with AXS-05 Treatment									
N	141	136	131	124	118	112	95	91	83
Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire									
Change from Baseline	-2.0	-4.4	-6.6	-7.5	-8.5	-8.7	-9.5	-9.4	-8.5
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Montgomery-Asberg Depression Rating Scale Total Score									
Change from Baseline	-9.1	-13.3	-16.8	-20.4	-22.1	-22.1	-23.2	-23.3	-24.5
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Hamilton Anxiety Rating Scale									
Change from Baseline	-3.4	-5.5	-7.4	-8.6	-9.4	-9.4	-10.2	-10.2	-10.2
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Sheehan Disability Scale									
Change from Baseline	-2.9	-5.0	-6.7	-8.3	-9.5	-9.7	-10.1	-10.8	-10.8
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: P values are not adjusted for multiplicity

Safety and Tolerability

Adverse Events in ≥ 5% of Individuals	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%)

- The safety population included all individuals who received at least 1 dose of AXS-05
- Long-term treatment with AXS-05 was generally well tolerated
- COVID-19 infection, nausea, and headache were the most common AEs
- Discontinuation rate due to AEs was 8.9%
- Serious adverse events occurred in 5 individuals (3.4%) after long-term treatment with AXS-05. No SAE occurred in more than 1 individual

Conclusions

- Treatment with AXS-05 rapidly improved depression and its associated symptoms, including cognitive and physical functioning and anxiety
- Treatment effects with AXS-05 were durable
- Long-term treatment with AXS-05 was generally well tolerated
- These data provide additional evidence for the efficacy of AXS-05 in MDD including indiviudals with prior treatment failures

Disclosures: *Amanda Jones is no longer affiliated with Axsome. Maurizio Fava is a consultant to Axsome. CS, ZT, SA, and HT are employees of Axsome Therapeutics.

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