# Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder: Results from the ASCEND Trial

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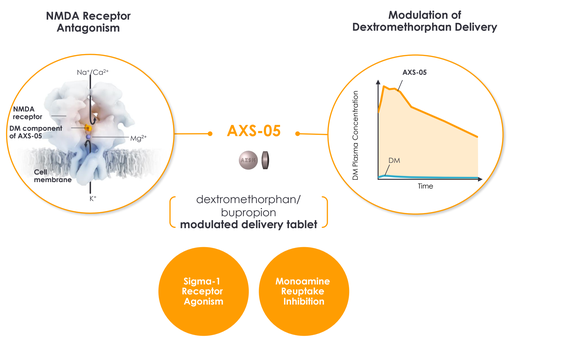
AXSOME THERAPEUTICS

## Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling, prevalent, and life-threatening, biologically-based disorder, and a leading cause of suicide[1,2]
- **MDD is difficult to treat:** 63% of MDD patients experience an inadequate response to current first-line therapies (STAR*D trial results), and the majority of these inadequate responders also fail second-line treatment (69%)[3]
- **Response to treatment takes time:** Current oral antidepressants are associated with prolonged time to clinically meaningful response (up to 6-8 weeks)[3]
- **Need for mechanistically novel approaches:** Currently approved oral antidepressants work primarily through monoaminergic mechanisms[4]
- **There is an urgent clinical need for:** New, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments[1,2]
- **Dysfunctional glutamatergic neurotransmission:** has been implicated in the pathophysiology of MDD, based on clinical and preclinical evidence, suggesting a potential role for NMDA receptor antagonism in the treatment of MDD[1,4]
- **NMDA receptor antagonism:** may result in improved antidepressant response and faster onset of action[1,4]
- **Activation of AMPA receptors:** induced by NMDA receptor blockade induces downstream cascades involved in neural plasticity that may underlie antidepressant-like effects[5,6,7]

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




Abbreviations: DM = dextromethorphan; NMDA = N-methyl-D-aspartate.

**AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:**[1,8]

- 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]

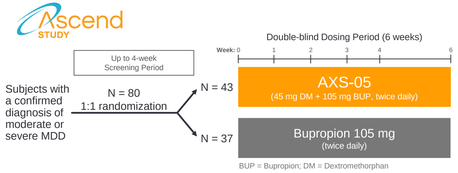
## References

**1.** Kadriu B, et al. Int J Neuropsychopharmacol. 2019;22(2):119-135. **2.** Substance Abuse and Mental Health Services Administration (SAMHSA) (2020). **3.** Rush AJ, et al. Am J Psychiatry. 2006;163:1905-1917. **4.** Machado-Vieira R, et al. Prog Neurobiol. 2017;152:21-37. **5.** Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press; 2013. **6.** Zarate Niciu MJ, et al. J Neural Transm (Vienna). 2014;121(8):907-924. **7.** Freudenberg F, et al. Neurosci Biobehav. Rev. 2015;52:193-206. **8.** Stahl SM. CNS Spectr. 2019 Oct:24(5):461-466.

## Trial Objective

The objective of the ASCEND trial was to evaluate the efficacy and safety of AXS-05, as compared to the active comparator bupropion, in patients with moderate or severe MDD

## Trial Design




BUP = Bupropion; DM = Dextromethorphan

- The ASCEND (Assessing Clinical Episodes in Depression) study was a Phase 2, randomized, double-blind, active-controlled, multicenter, U.S. trial
- 80 patients with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were randomized to receive AXS-05 (45 mg dextromethorphan/105 mg bupropion) (n=43), or bupropion (105 mg) (n=37), twice daily for 6 weeks. Prespecified efficacy analyses were conducted on this population on an intent-to-treat basis
- Patients without a confirmed diagnosis of moderate to severe MDD but who met all other entry criteria (n=17) were randomized for assessment of safety to maintain the blinding of study investigators, as prespecified

**Primary Endpoint:**

- The primary endpoint was the change from baseline in the MADRS total score, calculated at each time point in the study and averaged (overall treatment effect).

**Secondary Outcomes included:**

- Clinical Remission on the MADRS
- MADRS-6
- Clinical Global Impression-Improvement (CGI-I)
- Clinical Global Impression-Severity (CGI-S)
- Safety and tolerability

**Key inclusion criteria:**

- Male or female 18-65 years of age
- DSM-5 criteria for current MDD without psychotic features
- MADRS total score of ≥ 25
- CGI-S score of ≥ 4 at baseline

**Key exclusion criteria included:**

- History ECT, vagus nerve stimulation, TMS 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

### Demographics and Baseline Characteristics

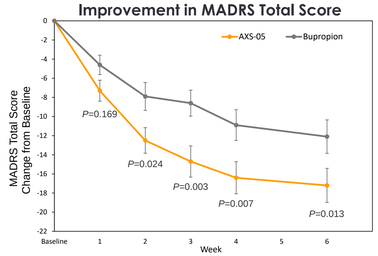
| | AXS-05 (45 mg DM / 105 mg BUP) (n = 43) | Bupropion (105 mg) (n = 37) |
|---|---|---|
| **Demographics** | | |
| **Age (years)** | 37.3 (11.94) | 37.7 (11.85) |
| **Female Gender, n (%)** | 25 (58.1%) | 26 (70.3%) |
| **Race, n (%)** | | |
| ***White*** | 30 (69.8%) | 20 (54.1%) |
| ***Black or African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

Data are mean (SD) unless otherwise stated.
BUP = bupropion; CGI-S = Clinical Global Impression – Severity; DM = dextromethorphan; MADRS = Montgomery-Åsberg Depression Rating Scale

- Baseline disease severity represents a moderate-to-severely depressed population
- 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

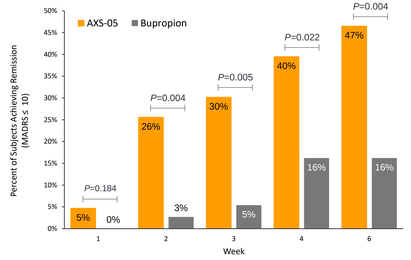
## Results

### Improvement in MADRS Total Score




- AXS-05 achieved the primary endpoint demonstrating a statistically significant mean reduction from baseline in the MADRS total score, calculated at each timepoint in the study and averaged, of 13.7 points for AXS-05 compared to 8.8 for bupropion (p<0.001)
- AXS-05 rapidly reduced depressive symptoms demonstrating numerical superiority to bupropion as early as Week 1, and statistically significant superiority at every timepoint thereafter including a 17.2 point reduction in the MADRS total score versus a 12.1 point reduction for bupropion (p=0.013) at Week 6

### Early and Sustained Remission




- Clinical remission, defined as a MADRS total score ≤10, was achieved by 47% of AXS-05 patients compared to 16% of bupropion patients (p=0.004)
- Remission rates were numerically greater for AXS-05 as compared to bupropion as early as Week 1, and statistically significantly greater at Week 2 (26% vs. 3%; p=0.004) and at every timepoint thereafter

### Improvement in Core Symptoms (MADRS-6)

**P-values over Time for Improvement of AXS-05 over Bupropion on MADRS-6**

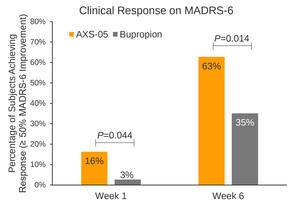
| Study Week | P-value |
|---|---|
| **Week 1** | 0.162 |
| **Week 2** | 0.027 |
| **Week 3** | 0.003 |
| **Week 4** | 0.008 |
| **Week 6** | 0.007 |

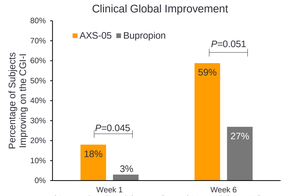
- The MADRS-6 is the sum of 6 of the 10 MADRS items described as the core symptoms of depression[1,2]
- AXS-05 significantly improved the core symptoms of depression, as measured by the MADRS-6, versus bupropion, demonstrating a 12.58 point reduction in the MADRS-6 subscale compared to an 8.70 point 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 timepoint thereafter

[1] Thase et al. *Int J Psychiatry Clin Pract.* 2012 Jun;16(2):121-31; [2] Bech P. *Dialogues Clin Neurosci.* 2006;8(2):207-15

### Rapid and Sustained Antidepressant Effect

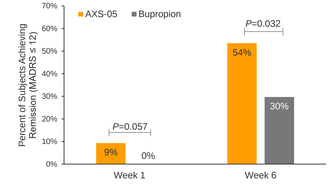
**Statistically Significant Antidepressant Activity as Early as Week 1 (Earliest Assessment)**




- As early as Week 1, AXS-05 treatment resulted in a statistically significantly greater proportion of patients experiencing a clinical response on the MADRS-6 (≥ 50% improvement) as compared to bupropion (p=0.044)
- The improvement over bupropion increased over time with statistical significance maintained at Week 6 (response rates of 63% for AXS-05 and 35% for bupropion, p=0.014)
- 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)

### Achievement of Remission Using MADRS Total Score ≤ 12




- As early as Week 1, AXS-05 treatment resulted in greater proportion of subjects achieving clinical remission (defined as a MADRS total score of ≤ 12), as compared to bupropion (9% versus 0%, p=0.057)
- Remission rates at Week 6 were statistically significantly greater for AXS-05 than for bupropion (54% versus 30%, p=0.032)

### Safety and Tolerability

- AXS-05 was safe and well tolerated in this trial with similar overall rates of adverse events 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
- AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction

## 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**