Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder: Results of a Phase 2, Double-Blind, Active-Controlled Trial

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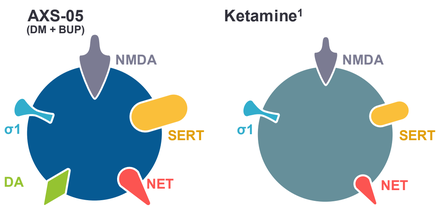
Introduction

- Major depressive disorder (MDD) is a disabling, chronic and prevalent condition.[1] MDD is the leading cause of suicide in the U.S.[2]
- Current antidepressants are associated with a high rate of inadequate response (as much as 70%), and prolonged time to clinically meaningful response (up to 6-8 weeks).[1] All currently approved oral MDD agents work primarily through monoaminergic mechanisms.[3]
- 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.[2,3]
- NMDA receptor blockade may result in improved antidepressant response and faster onset of action.[2,3]
- Activation of AMPA receptors induced by NMDA receptor blockade induces downstream cascades involved in neural plasticity that may underlie antidepressant-like effects.[4,5,6]
- AXS-05 (dextromethorphan and bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.[2]

[1]Rush AJ, et al. *Am J Psychiatry*. 2006; 11(163):1905-1917.
[2]Kadriu B, et al. *Int J Neuropsychopharmacol*. 2019;22(2):119-135.
[3]Machado-Vieira R, et al. *Prog Neurobiol*. 2017;152:21-37.
[4]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[5]Zarate Niciu MJ, et al. *J Neural Transm (Vienna)*. 2014;121(8):907-924.
[6]Freudenberg F, et al. *Neurosci Biobehav*. Rev. 2015;52:193-206.

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

- *NMDA receptor antagonism* – DM component of AXS-05.
- *Sigma-1 receptor agonism* – DM component of AXS-05.
- *Triple-reuptake inhibition (serotonin, norepinephrine, dopamine)* – DM and bupropion components of AXS-05.
- *Modulation of DM plasma concentrations* – Bupropion component of AXS-05 increases DM concentrations into potentially therapeutic range.



	DM	Ketamine	Assay
NMDA receptor binding (IC_{50})	402 nM	1047 nM	• Rat cerebellar granule neurons[2]
Sigma-1 agonist activity (K_i)	150 nM	140 μM	• Rat cerebellum[3] or PC12 cells[4]
Serotonin reuptake inhibition (K_i)	23 nM	162 μM	• Rat brain synaptosomes[5] • Human kidney cells[6]
Norepinephrine reuptake inhibition (K_i)	240 nM	67 μM	• Rat brain synaptosomes[5] • Human kidney cells[6]

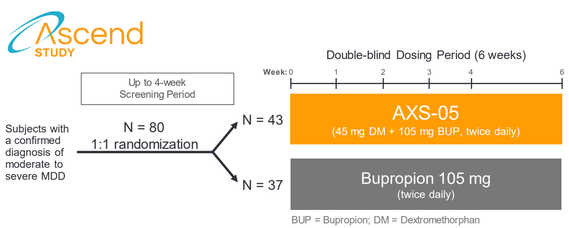
[1] Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2] Berman FW, et al. *J Biochem Toxicol*. 1996;11(5):217-226.
[3] Werling LL, et al. *Exp Neurol*. 2007;207(2):248-257.
[4] Robson MJ, et al. *Eur Neuropsychopharmacol*. 2012;22(4):308-317.
[5] Taylor CP, et al. *Pharmacol Ther*. 2016;164:170-182.
[6] Nishimura M, et al. *Anesthesiology*.1998;88(3):768-774.

Analysis courtesy of Dr. Stephen M. Stahl

Abbreviations: BUP = Bupropion; DA = Dopamine; DM = Dextromethorphan; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate; SERT= Serotonin Reuptake Transporter; σ1 = Sigma-1 Receptor

Methods

Objective: To evaluate the efficacy and safety of AXS-05 versus the active comparator, bupropion, in the treatment of MDD.



- The ASCEND (Assessing Clinical Episodes in Depression) study was a Phase 2, randomized, double-blind, active-controlled, multicenter, U.S. trial.
- Patients, 18-65 years of age inclusive, were required to meet the DSM-5 criteria for current MDD without psychotic features, and to have a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥ 25 and CGI-S score of ≥ 4 at baseline.
- 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.
- Exclusion criteria included: history of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation 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.
- 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 endpoints included MADRS-6, Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), remission, safety and tolerability.
- Primary and secondary efficacy comparisons were based on the least squares mean difference between AXS-05 and bupropion treatment groups.

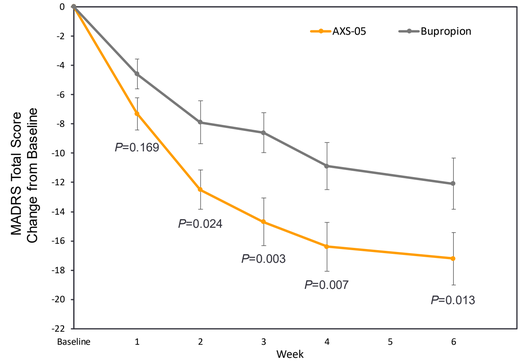
Demographics & Baseline Characteristics

	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

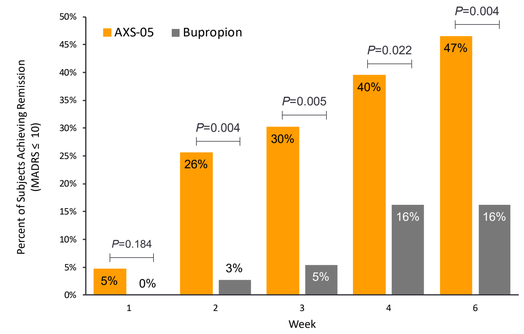
- Demographics and baseline clinical characteristics were similar across both treatment groups.
- 23% of subjects had received prior first line treatment in their current major depressive episode.
- Study completion rates were >70% in both treatment groups.

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 & 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

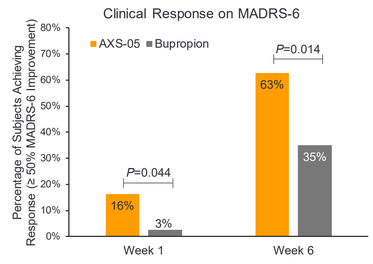
Study Week	P-value
Week 1	0.162
Week 2	0.027
Week 3	0.003
Week 4	0.008
Week 6	0.007

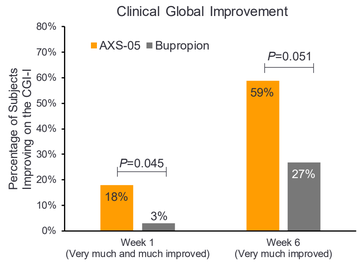
- The MADRS-6 is the sum of six of the 10 MADRS items that have been described as the core symptoms of depression.[1,2]
- AXS-05 significantly improved the core symptoms of depression, as measured by the MADRS-6, versus bupropion, demonstrating a 12.58 point reduction in the MADRS-6 subscale compared 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 time point 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 & Sustained Antidepressant Effect

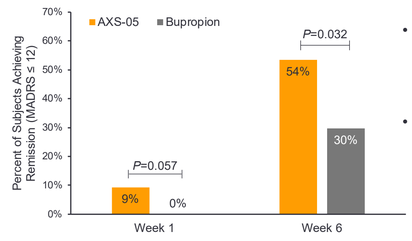
Statistically Significant Antidepressant Activity as Early as Week 1 (Earliest Assessment)





- 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 & Tolerability

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

Conclusion

- 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.
- The novel mechanism of action of AXS-05 was associated with a differentiated clinical profile as compared to currently approved agents for MDD.

Disclosure: AA, MJ, AJ, KK (former), COG & HT are full-time employees of Axsome Therapeutics. DVI is a consultant to Axsome Therapeutics.