Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist With Multimodal Activity, in Major Depressive Disorder: Results From the GEMINI Phase 3, Double-Blind, Placebo-Controlled Trial

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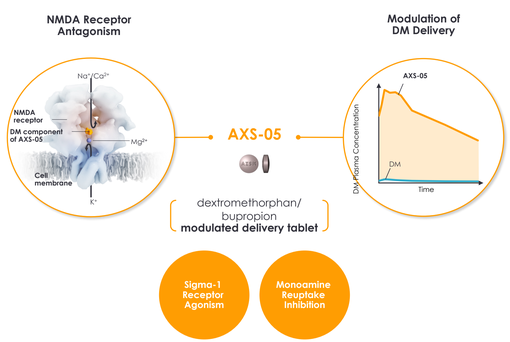
Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling and life-threatening, biologically-based disorder, as a leading cause of suicide[1]
- **MDD is highly prevalent:** Over 17 million adults in the United States experience at least one major depressive episode in a given year[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 (69%) 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]

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



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

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:[1,5] AXS-05 targets both glutamatergic (NMDA and sigma-1) and monoaminergic (serotonin, norepinephrine, dopamine) pathways[5]

- The DM component of AXS-05 is an NMDA receptor antagonist, sigma-1 receptor agonist, and an inhibitor of the serotonin and norepinephrine transporters[5]
- The bupropion component of AXS-05 serves to increase the bioavailability of DM and is a norepinephrine and dopamine reuptake inhibitor[6]
- Both DM and bupropion are nicotinic acetylcholine receptor antagonists and have anti-inflammatory properties[7,8]

References

1. Kadriu B, et al. Int J Neuropsychopharmacol. 2019;22(2):119-135. **2.** National Survey on Drug Use and Health (NSDUH). (2017). **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.** Anderson, A et al. 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. Poster presented at the 2019 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 28-31, 2019; Scottsdale, AZ. **6.** O'Gorman, C et al. AXS-05 for neuropsychiatric disorders: scientific rationale and clinical development. Poster presented at the 2018 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 29-June 1, 2018; Miami Beach, FL. **7.** Carroll FI, et al. Adv Pharmacol. 2014;69:177-216. **8.** Damaj MI, et al. J Pharmacol Exp Ther. 2005;312(2):780-785.

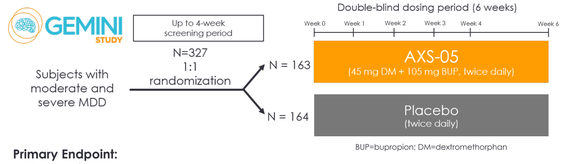
Trial Objective

The objective of the GEMINI Phase 3 trial was to evaluate the efficacy and safety of AXS-05 as compared to placebo in patients with moderate or severe MDD

Trial Design

- The GEMINI trial was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, U.S. trial
- Patients with a confirmed diagnosis of moderate-to-severe MDD were randomized 1:1) to receive either AXS-05 (45 mg DM/105 mg bupropion) (n=163), or placebo (n=164), twice daily for 6 weeks

GEMINI Phase 3 Trial Design



BUP=bupropion; DM=dextromethorphan

Primary Endpoint:
- Change from baseline in the MADRS total score at week 6

Key Secondary Endpoints:
- MADRS change at week 1 and week 2
- MADRS remission (≤10) at week 6
- MADRS response (≥50%) at week 6

Other Secondary Endpoints:
- Clinical Global Impression of Improvement (CGI-I)
- CGI- Severity (CGI-S)
- Patient Global Impression of Improvement (PGI-I)
- Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16)
- Sheehan Disability Scale (SDS)
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF)

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

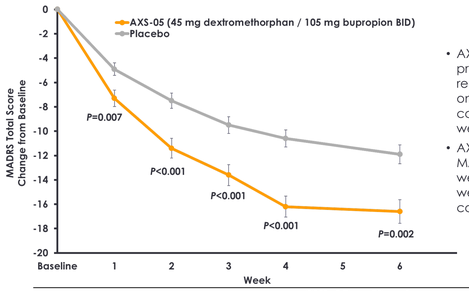
	AXS-05 (45 mg DM / 105 mg BUP)	Placebo
Age (years)	42.1 (12.71)	41.1 (13.78)
Female gender, n (%)	98 (60.1%)	117 (71.3%)
Race, n (%)		
White	88 (54.0%)	92 (56.1%)
Black or African American	61 (37.4%)	55 (33.5%)
BMI (mg/kg²)	29.2 (5.59)	29.4 (5.66)
MADRS total score	33.6 (4.43)	33.2 (4.36)
CGI-S Score	4.6 (0.59)	4.6 (0.57)

Data are mean (SD) unless otherwise stated.

- Baseline disease severity represents a moderate-to-severely depressed population
- Demographics were similar across both AXS-05 and placebo treatment groups

Results

Rapid and Robust Improvement in Symptoms of Depression

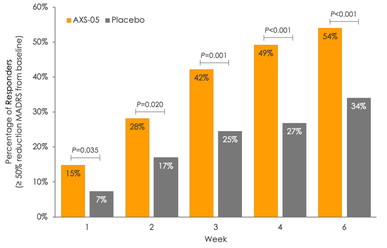


- AXS-05 achieved the primary endpoint - mean reduction from baseline on the MADRS total score compared to placebo at week 6 (p=0.002)
- AXS-05 rapidly reduced MADRS total score by week 1 (p=0.007) and week 2 (p<0.001) compared with placebo

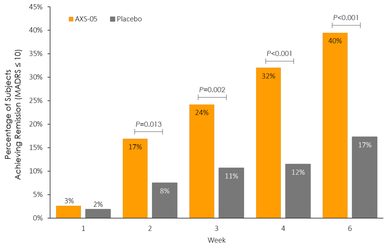
	AXS-05 (n=156)	Placebo (n=162)	Difference	P-Value
Primary Endpoint Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
Key Secondary Endpoint Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007

Notes: P-values calculated from LSMean. Abbreviations: BID=twice daily

Rapid Achievement of Clinical Response and Sustained Remission



Clinical Response (≥50% MADRS)
- AXS-05 treatment resulted in significantly greater rates of clinical response compared to placebo at week 1 (p=0.035) and week 2 (p=0.020)
- Statistical significance was maintained at all timepoints over the course of the 6- week study



Clinical Remission (MADRS ≤10)
- Greater rates of clinical remission with AXS-05 compared to placebo as early as week 2 (p<0.013)
- Statistical significance maintained at all timepoints with increasing separation from placebo out to week 6 (p<0.001)

Rapid and Durable Antidepressant Effects Across Multiple Outcomes

	AXS-05 vs Placebo		
	Week 1	Week 2	Week 6
Depressive Symptom Improvement			
CGI-I % with marked/moderate improvement	22% vs 13% p=0.035	44% vs. 22% p=<0.001	58% vs. 43% p=0.016
CGI-S Improvement from baseline	0.7 vs. 0.4 p=0.013	1.1 vs 0.7 p=<0.001	1.7 vs. 1.2 p=0.002
PGI-I % Reporting very much/much improved	14% vs. 5% p=0.008	30% vs. 18% p=0.015	47% vs. 31% p=0.007
Quality of Life and Functional Improvement			
Q-LES-Q-SF Improvement from baseline as % of maximum possible score	9.1 vs 5.8 p=0.031	13.2 vs 8.9 p=0.017	19.8 vs. 14.4 p=0.011
SDS total score Improvement from baseline	4.6 vs. 3.4 ns	6.8 vs. 4.5 p=0.003	9.0 vs. 6.3 p=0.002

- Rapid onset of action with AXS-05, evidenced by early and highly statistically separation from placebo on numerous endpoints
- AXS-05 was statistically significantly superior to placebo on multiple measures at 1 week, the earliest time point assessed
- Rapid therapeutic effect was durable and maintained out to 6 weeks, with statistically significant effects on multiple outcome measures
- Significant improvements in both daily functioning as measured by the SDS, and quality of life as measured by the Q-LES-Q-SF

Safety and Tolerability

	AXS-05 (N=162)	Placebo (N=164)
Any Treatment-emergent AE*	**100 (61.7%)**	**74 (45.1%)**
Dizziness	26 (16.0%)	10 (6.1%)
Nausea	21 (13.0%)	14 (8.5%)
Headache	13 (8.0%)	6 (3.7%)
Diarrhea	11 (6.8%)	5 (3.0%)
Somnolence	11 (6.8%)	5 (3.0%)
Dry mouth	9 (5.6%)	4 (2.4%)

AE = adverse events
*Adverse events occurring in ≥5% of subjects treated with AXS-05

- Most commonly reported AEs were dizziness, nausea, and headache
- Rates of discontinuation due to AEs were low in both groups, 6.2% for AXS-05 and 0.6%, for placebo
- One serious AE (pancreatitis) was observed in the AXS-05 group, which was deemed not related to study drug

Conclusions

- **AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity representing a mechanistically novel approach for the treatment of major depressive disorder**
- **AXS-05 treatment resulted in rapid, substantial, sustained, and statistically significant improvement in symptoms of depression as compared to placebo**
- **Statistically significant improvement as compared to placebo demonstrated at week 1, the earliest time point measured, for multiple outcome measures, including MADRS, clinical response, patient and clinician global measures, and quality of life**
- **AXS-05 was safe and generally well-tolerated in this trial, with the most commonly reported adverse events being dizziness, nausea, and headache**
- **AXS-05 was not associated with psychotomimetic effects, increased sexual dysfunction, or weight gain**

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Disclosures: COG, AJ and HT are employees of Axsome Therapeutics. DVI is a consultant to Axsome Therapeutics.