# 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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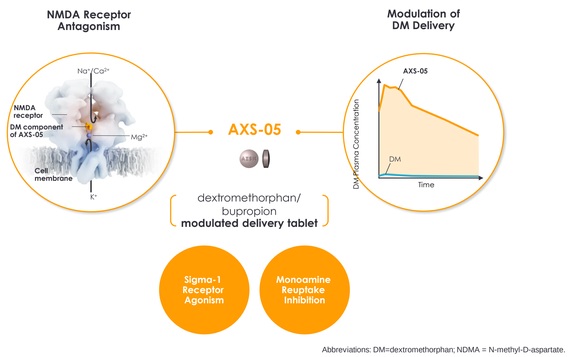
## Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling and life-threatening, biologically-based disorder, and a leading cause of suicide[1]
- **MDD is highly prevalent:** Over 19 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 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.** 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.** 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.

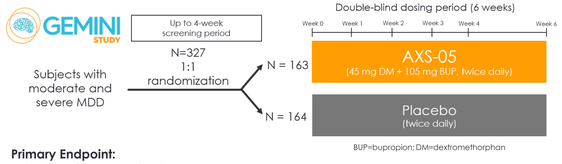
## Trial Objective

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 or 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

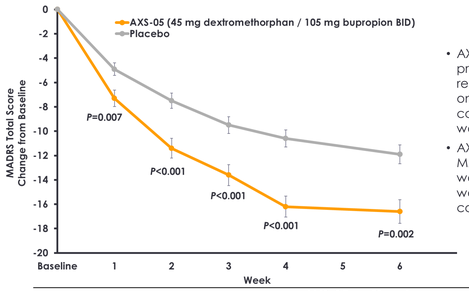
| | AXS-05 (45 mg DM / 105 mg BUP) | Placebo |
|---|---|---|
| **Age (years)** | 42.1 (12.71) | 41.1 (13.78) |
| **Female gender, n (%)** | 98 (60.1%) | 117 (71.3%) |
| **Race, n (%)** | | |
| **White** | 88 (54.0%) | 92 (56.1%) |
| **Black or African American** | 61 (37.4%) | 55 (33.5%) |
| **BMI (mg/kg²)** | 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

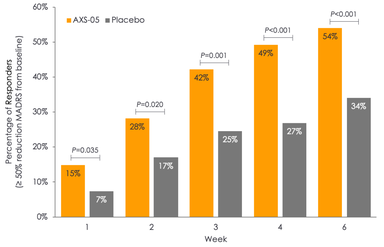



- AXS-05 achieved the primary endpoint - mean reduction from baseline on the MADRS total score compared to placebo at week 6 ($p$=0.002)
- AXS-05 rapidly reduced MADRS total score by week 1 ($p$=0.007) and week 2 ($p$<0.001) compared to placebo

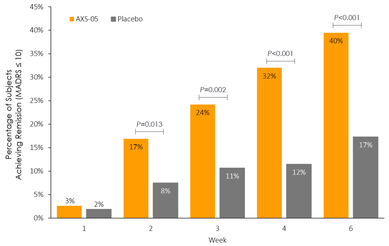
| | AXS-05 (n=156) | Placebo (n=162) | Difference | P-Value |
|---|---|---|---|---|
| **Primary Endpoint** Change in MADRS Total Score at Week 6 | -16.6 | -11.9 | -4.7 | 0.002 |
| **Key Secondary Endpoint** Change in MADRS Total Score at Week 1 | -7.3 | -4.9 | -2.4 | 0.007 |

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 Change 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 Change from baseline in % 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 change 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, SF, AJ, CS, and HT are employees of Axsome Therapeutics. DVI is a consultant to Axsome Therapeutics.