Effects of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, on Patient Reported Depressive Symptoms in Major Depressive Disorder: Results from the GEMINI Phase 3 Double-Blind, Placebo-Controlled Trial

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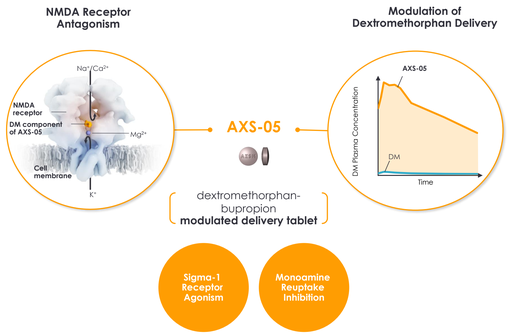
Introduction: Evaluation of Patient-Reported Depression Outcomes with AXS-05

- **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 oral 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]
- **Patient reported outcomes (PROs) in depression:** A PRO is directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's symptoms, quality of life, or functional status associated with treatment.[4] PROs therefore provide an assessment of the benefit felt by patients as a direct result of an intervention
- In the Phase 3 GEMINI trial of AXS-05 in the treatment of MDD, two PROs for depression were used: The Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16), and the Patient Global Impression of Improvement (PGI-I) for depression. The QIDS-16 is a well-established patient reported tool and was the primary outcome measure used in the STAR*D trial[5]
- The PROs in the GEMINI trial complement the clinician-reported measures, including the MADRS, used in this trial

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:[1,6]

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist[6]
- 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[6]

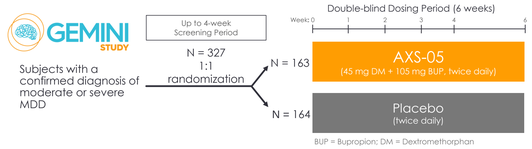
References

1. Kadriu B, et al. Int J Neuropsychopharmacol. 2019;22(2):119-135. **2.** Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. **3.** Rush AJ, et al. Am J Psychiatry. 2006;163:1905-1917. **4.** Ishak WW, et al. Dialogues Clin Neurosci. 2014;16:171-183. **5.** Rush AJ, et al. Biol Psychiatry. 2003;54(5):573-583. **6.** Stahl SM. CNS Spectr. 2019;24(5):461-466.

Objective and Design of the Phase 3 GEMINI Trial of AXS-05 in MDD

- 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
- 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 dextromethorphan-105 mg bupropion) (n=163), or placebo (n=164), twice daily for 6 weeks

GEMINI Phase 3 Trial Design



BUP = Bupropion; DM = Dextromethorphan

- This presentation focuses on the effect of AXS-05 on patient-reported outcomes of depression using a symptom-specific assessment (the QIDS-SR-16), and a global assessment (the PGI-I)
- The QIDS-SR-16 is a 16-item, patient-reported scale which evaluates nine DSM-IV symptom criterion domains: 1) sad mood; 2) concentration; 3) self-criticism; 4) suicidal ideation; 5) interest; 6) energy/fatigue; 7) sleep disturbance (initial, middle, and late insomnia or hypersomnia); 8) decrease or increase in appetite or weight; and 9) psychomotor agitation or retardation. The total score ranges from 0 to 27
- The PGI-I scale is a patient-rated scale that is used to rate total improvement or worsening of depression. The patient rates on a scale from "very much improved" to "very much worse"

Primary Endpoint:
- Change from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score at week 6

Patient Reported Depression Outcomes:
- Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16)
- Patient Global Impression of Improvement (PGI-I)

Other Secondary Endpoints:
- Clinical Global Impression of Improvement (CGI-I)
- Clinical Global Impression of Severity (CGI-S)
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF)
- Sheehan Disability Scale (SDS)

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

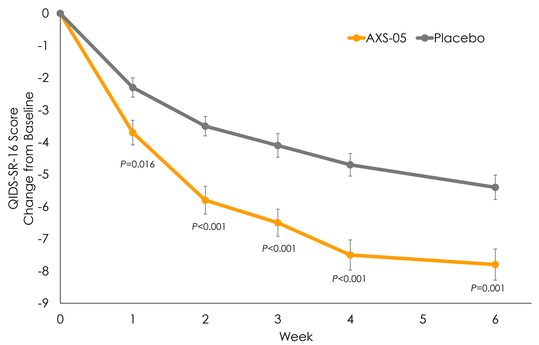
	AXS-05 (45 mg DM / 105 mg BUP)	Placebo
Age (years)	42.1 (12.71)	41.1 (13.78)
Female gender, n (%)	98 (60.1%)	117 (71.3%)
Race, n (%)		
White	88 (54.0%)	92 (56.1%)
Black or African American	61 (37.4%)	55 (33.5%)
BMI (mg/kg²)	29.2 (5.59)	29.4 (5.66)
MADRS total score	33.6 (4.43)	33.2 (4.36)
CGI-S Score	4.6 (0.59)	4.6 (0.57)
QIDS-SR-16	16.2 (3.72)	15.8 (4.05)

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

BMI = body mass index, BUP = bupropion, CGI-S = clinician global impression-severity, DM = dextromethorphan, MADRS = Montgomery–Åsberg Depression Rating Scale, QIDS-SR-16 = Quick Inventory Depressive Symptoms-Self Report-16 item. Data are mean (SD) unless otherwise stated.

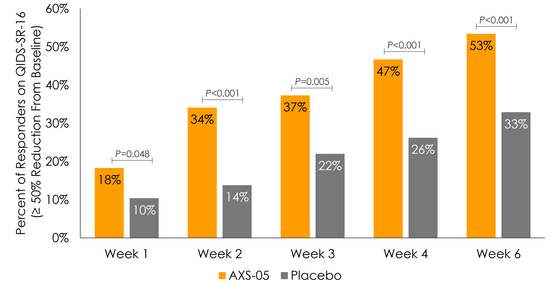
Results: Effects of AXS-05 on Patient-Reported Depression Outcomes

Improvement on Patient-Reported QIDS-SR-16



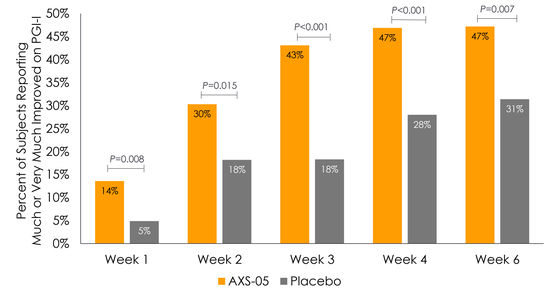
- Treatment with AXS-05 resulted in a rapid, substantial, and significant reduction in patient reported depressive symptoms as measured by the QIDS-SR-16
- Statistically significant treatment effects were observed at Week 1, the earliest time point assessed, and were sustained through Week 6

Clinical Response on the QIDS-SR-16 (≥50% Improvement)



- Patients receiving AXS-05 had significantly greater rates of clinical response on the QIDS-SR-16 compared to placebo starting at Week 1 (p=0.048) and which were maintained through Week 6 (p<0.001)
- Nearly 50% of patients treated with AXS-05 achieved clinical response by Week 4 (p<0.001 vs. placebo)

Patient-Reported Global Improvement



- As early as Week 1, a statistically significantly greater proportion of patients receiving AXS-05 reported their depression as "very much" or "much" improved as compared to patients receiving placebo, with the effect maintained through Week 6

Results: Effects of AXS-05 on Clinician-Rated Depression Outcomes

Improvements on Clinician-Rated Outcomes

	AXS-05 vs Placebo		
	Week 1	**Week 2**	**Week 6**
Depressive Symptom Improvement			
MADRS Total (Primary & Key Secondary Endpoints) Change from baseline	7.3 vs. 4.9 p=0.007	11.4 vs. 7.5 p<0.001	16.6 vs. 11.9 p=0.002
MADRS Response % with ≥ 50% change from baseline	15% vs. 7% p=0.035	28% vs. 17% p=0.020	54% vs. 34% p<0.001
Global Outcome Measures			
CGI-I % with marked/moderate improvement	22% vs. 13% p=0.035	44% vs. 22% p<0.001	58% vs. 43% p=0.016

Safety and Tolerability

- AXS-05 was generally safe and well tolerated with the most commonly reported adverse events being dizziness, nausea, and headache
- Rates of discontinuation due to adverse events were low in both groups, 6.2% for AXS-05 and 0.6%, for placebo

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**
- **Treatment with AXS-05 resulted in rapid, substantial, and statistically significant improvement in patient-reported depression outcomes, measured using symptom-specific (QIDS-SR-16) and global (PGI-I) measures, starting at Week 1, the earliest time point assessed**
- **The improvements in the QIDS-SR-16 and PGI-I were maintained through Week 6**
- **The improvements in patient-reported measures were consistent with the observed improvements in clinician-reported measures (MADRS, CGI-I) with AXS-05 treatment**
- **AXS-05 was safe and generally well-tolerated in this trial, with the most commonly reported adverse events being dizziness, nausea, and headache**

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Disclosures: All co-authors are employees of Axsome Therapeutics.