EUROPEAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY 2020 ANNUAL MEETING, 12-15 SEPTEMBER 2020. POSTER P327.

Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder

Cedric O'Gorman[4], Amanda Jones[4], Dan V. Iosifescu[2,3], Maurizio Fava[1], Herriot Tabuteau[4]

[1]Massachusetts General Hospital & Harvard Medical School, Boston, MA; [2]NYU School of Medicine, New York, NY; [3]Nathan Kline Institute, Orangeburg, NY; [4]Axsome Therapeutics, New York, NY

AXSOME THERAPEUTICS

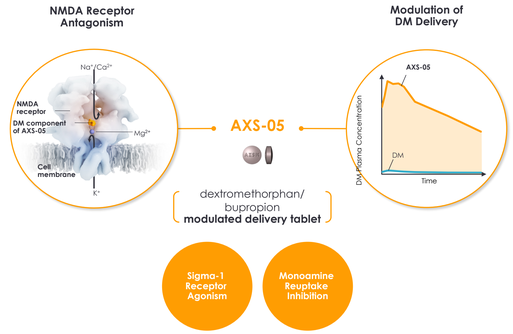
22 Cortlandt Street, New York, NY 10007, USA

For more information, please contact Cedric O'Gorman at **cogorman@axsome.com**

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

- **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] Globally, more than 264 million people of all ages suffer from depression[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]
- **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 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[6]
- AXS-05 targets both glutamatergic (NMDA and sigma-1) and monoaminergic (serotonin, norepinephrine, dopamine) pathways[6]
- The DM component of AXS-05 is an NMDA receptor antagonist, sigma-1 receptor agonist, and an inhibitor of the serotonin and norepinephrine transporters[6]
- 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]

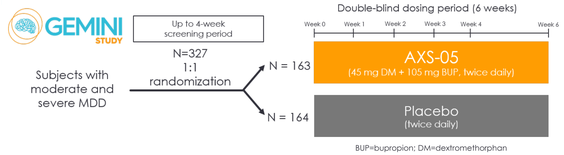
References

1. Kadriu B, et al. Int J Neuropsychopharmacol. 2019;22(2):119-135. 2. 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. 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.

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 DM/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

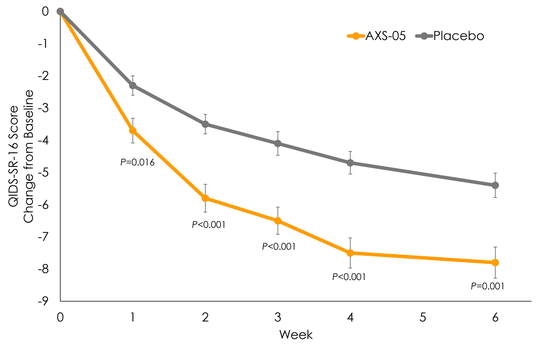
	AXS-05 (45 mg DM / 105 mg BUP)	Placebo
Age (years)	42.1 (12.71)	41.1 (13.78)
Female gender, n (%)	98 (60.1%)	117 (71.3%)
Race, n (%)		
White	88 (54.0%)	92 (56.1%)
Black or African American	61 (37.4%)	55 (33.5%)
BMI (mg/kg²)	29.2 (5.59)	29.4 (5.66)
MADRS total score	33.6 (4.43)	33.2 (4.36)
CGI-S Score	4.6 (0.59)	4.6 (0.57)
QIDS-SR-16	16.2 (372)	15.8 (4.05)

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.

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

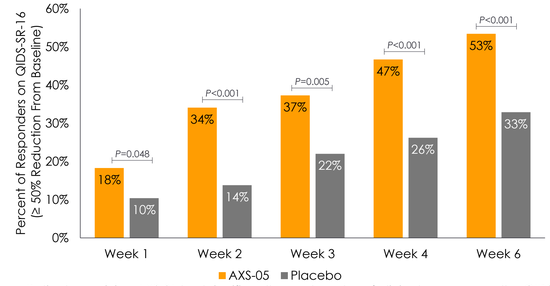
Results: Effects of AXS-05 on Patient-Reported Depression Outcomes

Rapid and Significant Improvement on Patient-Reported QIDS-SR-16



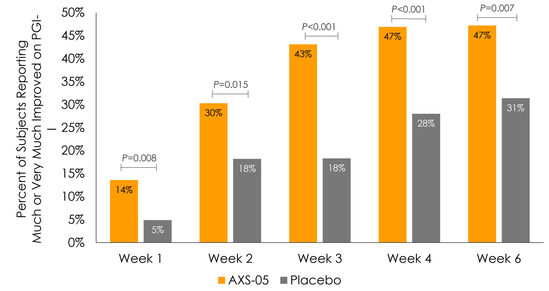
- Treatment with AXS-05 resulted in a rapid, substantial, and significant reduction in patient reported depressive symptoms as measured by the QIDS-SR-16
- Statistically significant treatment effects were observed at Week 1, the earliest time point assessed, and were sustained through Week 6

Rapid Achievement of 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)

Early and Sustained 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

Rapid and Significant 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 AEs being dizziness (16.0% AXS-05 vs. 6.1% placebo), nausea (13.0% vs. 8.5%), and headache (8.0% vs. 3.7%)
- Rates of discontinuation due to AEs were low in both groups, 6.2% for AXS-05 and 0.6%, for placebo

Conclusions

- **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**
- **AXS-05 was not associated with psychotomimetic effects, increased sexual dysfunction, or weight gain**
- **AXS-05 is an oral, investigational NMDA receptor antagonist and sigma-1 receptor agonist representing a mechanistically novel approach for the treatment of major depressive disorder**

Acknowledgments: We express our gratitude to the patients and clinical investigators for their participation in the study. This study was supported by Axsome Therapeutics.
Disclosures: COG, AJ and HT are employees of Axsome Therapeutics. DVI is a consultant to Axsome Therapeutics.