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Impact of AXS-05, an Oral NMDA Receptor Antagonist, on Anhedonic Symptoms in Major Depressive Disorder

Amanda Jones[3], Roger S. McIntyre[1,2], Mark Jacobson[3], Caroline Streicher[3], Zach Thomas[3], Herriot Tabuteau[3]

[1]University of Toronto, Toronto, CA; [2]Brain and Cognition Discovery Foundation, Toronto, CA; [3]Axsome Therapeutics, New York, NY,

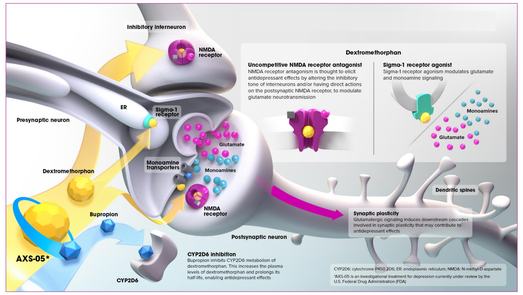
22 Cortlandt Street, 16th Floor
New York, NY 10007, USA

For more information, please contact Amanda Jones at **ajones@axsome.com**

Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling, prevalent, 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]
- **Anhedonia**, the inability to feel pleasure, is one of the core features of major depressive disorder (MDD) and is present in up to 75% of individuals diagnosed with MDD[4]
- **Anhedonia is considered among the most bothersome** aspects of MDD by patients, has been associated with decreased functioning and is a risk factor for non-response to antidepressant therapy [5,6]
- **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[7]
- **Glutamatergic hypothesis of MDD:** 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[1,7]
- **There is an urgent clinical need for:** New, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments[1]

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



AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:[1,8]

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist[8]
- 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[8]

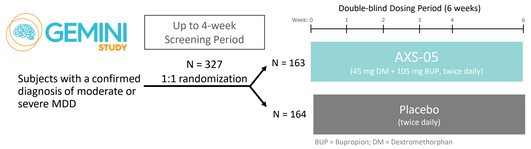
Objective

- **GEMINI** was a phase 3, randomized, double-blind, placebo-controlled, multi-center, U.S. trial, in which 327 adult patients with confirmed moderate to severe MDD were randomized to either AXS-05 or placebo (NCT04019704)
  - A *post-hoc* analysis was conducted to determine the impact of AXS-05 as compared to placebo on the 5-item MADRS anhedonia subscale
- **Objective:** To evaluate the effect of AXS-05 as compared to placebo in improving anhedonic symptoms in MDD as assessed by the MADRS anhedonia subscale

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.** Franken IH, et al. J Affect Disord 2007;99:83–9. **5.** Baune BT, et al. 2021;17:2995-3006. **6.** Wardenaar KJ, et al. J. Affect. Disord 2012; 136:1198–1203. **7.** Machado-Vieira R, et al. Prog Neuroboiol. 2017;152:21-37. **8.** Stahl SM. CNS Spectr. 2019;24:461-466. **9.** Cao et al. Front Psychiatry. 2019;10:17.

Study Design: GEMINI



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

Key Secondary Endpoints: Change from baseline and in MADRS at Week 1 and Week 2

MADRS Ahedonia Subscale: : Change from baseline and rate of response as measured by the **MADRS Anhedonia Subscale** which includes 5-items:

- Apparent sadness
- Reported sadness
- Concentration difficulties
- Lassitude
- Inability to feel

Previous research has demonstrated that the MADRS anhedonia subscale is highly correlated to the to the Snaith-Hamilton Pleasure Scale, a validated measure of hedonic tone[9]

Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
▪ 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	▪ History of 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

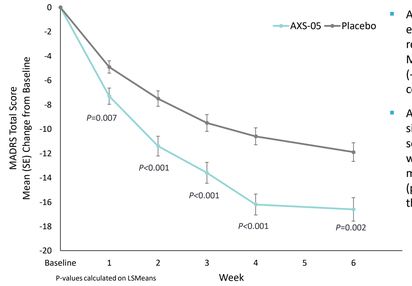
	AXS-05	Placebo
Demographics		
Age (years)	42.1 (12.71)	41.1 (13.78)
Female gender, n (%)	98 (60.1%)	117 (71.3%)
Race, n (%)		
White	88 (54.0%)	92 (56.1%)
Black or African American	61 (37.4%)	55 (33.5%)
Clinical Characteristics		
MADRS total score	33.6 (4.43)	33.2 (4.36)
MADRS Anhedonia score	19.8 (2.48)	19.6 (2.40)
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 control groups

Results

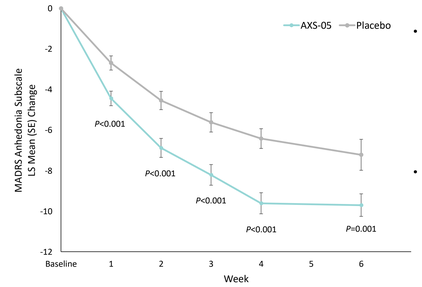
Improvement in Symptoms of Depression (MADRS Total) with AXS-05 Compared to Placebo



- AXS-05 achieved the primary endpoint – statistically significant reduction from baseline on the MADRS total score at week 6 (-16.6 vs. -11.9, p=0.002), compared to placebo
- AXS-05 rapidly and statistically significantly reduced MADRS total score compared to placebo, by week 1, the first timepoint measured (p=0.007), at week 2 (p<0.001), and at all timepoints thereafter

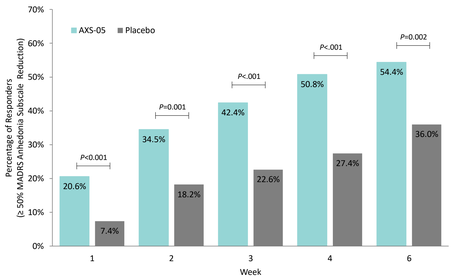
	AXS-05 (n=156)	Placebo (n=162)	Difference	*P*-Value
Key Secondary Endpoints				
Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007
Change in MADRS Total Score at Week 2	-11.1	-7.7	-3.4	<0.001

Improvement in Anhedonia with AXS-05 Compared to Placebo



- At Week 1 (the first timepoint measured) treatment with AXS-05 resulted in a statistically significant mean reduction from baseline in the MADRS anhedonia subscale score of 4.44, versus 2.69 points for placebo (p<0.001)
- By Week 6, the mean reduction from baseline in the MADRS anhedonia subscale was 9.70 for AXS-05 compared to 7.22 for placebo (p=0.001)

Response (≥ 50% Reduction) in MADRS Anhedonia Subscale



- Rates of response (≥ 50% MADRS anhedonia subscale improvement) were statistically significantly greater for AXS-05 compared to placebo at Week 1 (p<0.001) and at every timepoint thereafter
- Response was achieved by 54% of AXS-05 patients versus 36% of placebo patients at Week 6 (p=0.002)

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%)

- The most commonly reported AEs were dizziness, nausea, and headache
- Rates of discontinuation due to AEs were 6.2% for AXS-05 and 0.6%, for placebo

Conclusions

- AXS-05, a novel oral NMDA receptor antagonist, rapidly and statistically significantly improved anhedonic symptoms, as well as overall depressive symptoms
- Significant improvements in anhedonic symptoms with AXS-05 treatment were observed at Week 1 and at every timepoint thereafter
- AXS-05 was well tolerated
- These data support the efficacy of AXS-05 in a broad range of symptomatology in patients with MDD