Rapid Effects of AXS-05, an Oral NMDA Receptor Antagonist, in Major Depressive Disorder: Results From Two Randomized, Double-Blind, Controlled Trials

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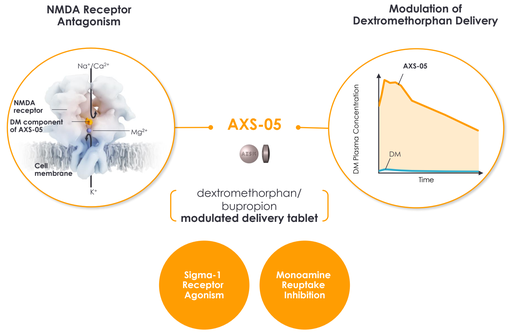
Introduction

- **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]
- **Delayed antidepressant treatment response** is associated with an increased risk of relapse, poorer long-term outcomes, and a decreased likelihood of functional improvement[3-5]
- **Need for mechanistically novel approaches:** Currently approved oral antidepressants work primarily through monoaminergic mechanisms[6]
- **There is an urgent clinical need for:** New, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments[1,2]
- **In this research:** Herein we analyze data from two randomized controlled trials to determine the effect of AXS-05, a novel, oral, investigational, NMDA receptor antagonist, on symptoms of MDD during the first 2 weeks of treatments

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:[1,7]

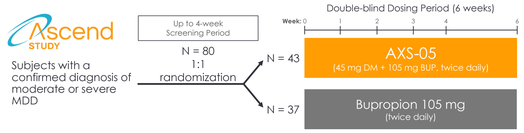
- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist[7]
- These actions modulate glutamatergic neurotransmission
- The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor[7]

References

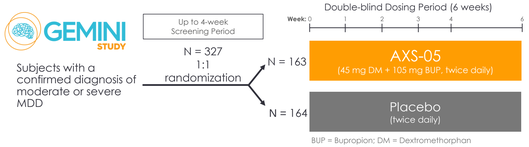
1. Kadriu B, et al. Int J Neuropsychopharmacol. 2019;22(2):119-135. **2.** Substance Abuse and Mental Health Services Administration (SAMHSA) (2020). **3.** Rush AJ, et al. Am J Psychiatry. 2006;163:1905-1917. **4.** Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. Cambridge University Press; 2013. **5**. Sheehan DV, et al. J Affect Disord. 2017;215:299-313. **6.** Machado-Vieira R, et al. Prog Neurobiol. 2017;152:21-37. **7.** Stahl SM. CNS Spectr. 2019 Oct;24(5):461-466.

Trial Objectives and Designs

- The objective of the ASCEND Phase 2 trial was to evaluate the efficacy and safety of AXS-05, as compared to the active comparator bupropion, in patients with moderate or severe 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



Key Inclusion and Exclusion Criteria for ASCEND and GEMINI

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 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

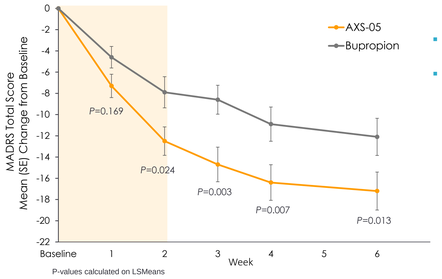
	GEMINI		ASCEND	
	AXS-05	Placebo	AXS-05	Bupropion
Demographics				
Age (years)	42.1 (12.71)	41.1 (13.78)	37.3 (11.94)	37.7 (11.85)
Female gender, n (%)	98 (60.1%)	117 (71.3%)	25 (58.1%)	26 (70.3%)
Race, n (%)				
White	88 (54.0%)	92 (56.1%)	30 (69.8%)	20 (54.1%)
Black or African American	61 (37.4%)	55 (33.5%)	12 (27.9%)	14 (37.8%)
Clinical Characteristics				
MADRS total score	33.6 (4.43)	33.2 (4.36)	31.8 (4.04)	32.2 (4.46)
CGI-S Score	4.6 (0.59)	4.6 (0.57)	4.4 (0.50)	4.5 (0.51)
SDS total score	20.3 (5.96	19.3 (5.82)	SDS was not assessed in ASCEND	
Q-LES-Q-SF total score (% maximum)	34 (13.46)	36 (12.29)	Q-LES-Q-SF was not assessed in ASCEND	

Data are mean (SD) unless otherwise stated. SDS = Sheehan Disability Scale. Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

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

Results

Rapid and Sustained Improvement in Symptoms of Depression with AXS-05 Compared to Bupropion (ASCEND)

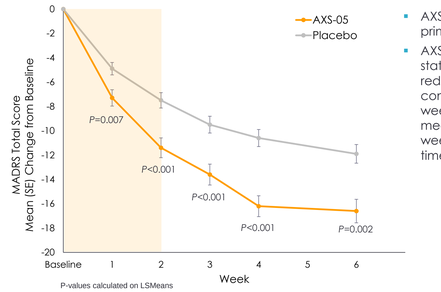


- AXS-05 achieved the primary endpoint (p<0.001)
- AXS-05 demonstrated rapid reduction in depressive symptoms with numerical superiority to bupropion as early as Week 1, and statistically significant superiority at Week 2 and all timepoints thereafter

	AXS-05 (n=43)	Bupropion (n=37)	Difference	*P*-Value
Primary Endpoint Overall change in MADRS Total Score	-13.7	-8.8	-4.9	<0.001
Secondary Endpoints Change in MADRS Total Score at Week 1	-7.4	-4.5	-2.9	0.169
Change in MADRS Total Score at Week 2	-12.5	-7.8	--4.7	0.024
Change in MADRS Total Score at Week 6	-17.3	-12.1	-5.2	0.013

- At Week 1, AXS-05 was superior to bupropion on: CGI-I (18% vs. 3%; p=0.045) and MADRS-6 response (≥50% improvement; 16% vs. 3%; p=0.044)
- From Week 2, AXS-05 was superior to bupropion on: mean MADRS improvement (12.5 vs. 7.8; p=0.024), MADRS remission (≤10; 26% vs. 3%; p=0.004), and CGI-S (1.41 vs. 0.9; p=0.049)

Rapid and Sustained Improvement in Symptoms of Depression with AXS-05 Compared to Placebo (GEMINI)



- AXS-05 achieved the primary endpoint (p=0.002)
- 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
Primary Endpoint Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
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

Rapid and Significant Antidepressant Effects Across Multiple Outcomes (GEMINI)

	AXS-05	Placebo	Difference	*P*-Value
Week One Clinical Global Impression – Improvement % with marked/moderate improvement	22%	13%	9%	0.035
Clinical Global Impression – Severity Change from baseline	0.7	0.4	0.3	0.013
Patient Global Impression– Improvement % Reporting very much/much improved	14%	5%	9%	0.008
Clinical Response (≥50% MADRS improvement)	15%	7%	8%	0.035
Quality of Life Improvement (Q-LES-Q-SF) Change from baseline in % of maximum possible score	9.1	5.8	3.3	0.031
Week Two Clinical Global Impression – Improvement % with marked/moderate improvement	44%	22%	22%	<0.001
Clinical Global Impression – Severity Change from baseline	1.1	0.7	0.4	<0.001
Patient Global Impression– Improvement % with marked/moderate improvement	30%	18%	12%	0.015
Clinical Remission (MADRS total score ≤10)	17%	8%	9%	0.013
Clinical Response (≥50% MADRS improvement)	28%	17%	11%	0.020
Quality of Life Improvement (Q-LES-Q-SF) Change from baseline in % of maximum possible score	13.2	8.9	4.3	0.017
Improvement in Functioning (SDS Total Score) Change from baseline	6.8	4.5	2.3	0.003

Safety and Tolerability

- AXS-05 was safe and well-tolerated in both trials
- In the two studies, the most commonly reported adverse events with AXS-05 were dizziness, nausea and headache
- Similar overall rates of adverse events were reported in the AXS-05 and bupropion treatment groups
- AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction

Conclusions

- **AXS-05, a novel oral NMDA receptor antagonist, rapidly and statistically significantly improved depressive symptoms at Weeks 1 and 2 in placebo- and active- controlled trials**
- **In both studies, rapid remission from depressive symptoms was achieved by Week 2 and maintained over the 6 week treatment period**
- **AXS-05 treatment resulted in rapid, substantial, sustained, and statistically significant improvement in depression, quality of life and functioning as compared to placebo in the GEMINI trial**
- **AXS-05 was statistically significantly superior to bupropion, a well-established antidepressant, in rapid and sustained improvements in depressive symptoms in the ASCEND trial**
- **The novel mechanisms of action of AXS-05 may contribute to these rapid antidepressant effects**