Rapid and Sustained Improvements in Quality of Life and Functioning with AXS-05, an Oral NMDA Receptor Antagonist, in Patients with Major Depressive Disorder

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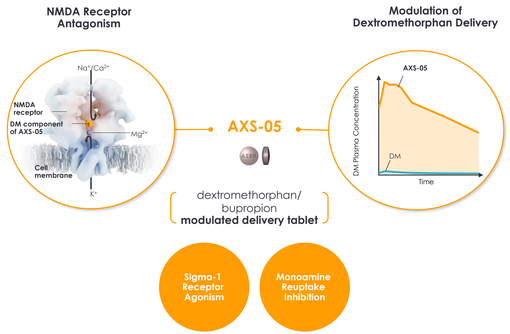
Introduction

- Major depressive disorder (MDD) is a leading cause of disability worldwide[1,2]
- Results of the STAR*D trial indicate that as much as 70% of patients with MDD experience an inadequate response to current first-line oral treatments, and that most of these patients also fail second line treatments[3]
- Epidemiological studies demonstrate that MDD significantly impacts quality of life (QoL) and functioning[4]
- With existing oral antidepressants, which are primarily monoaminergic-based, it can take 6-8 weeks to experience a clinically meaningful response in depressive symptoms, and improvements in QoL and functioning often lag behind symptomatic improvement[3,5,6]
- Early improvements in functioning are associated with an increased likelihood of achieving optimal functional outcomes[6]
- A return to one's premorbid level of functioning is a priority outcome for individuals suffering from MDD[7]
- Treatments that rapidly improve QoL and functioning, as well as depressive symptoms, are urgently needed

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



Abbreviations: DM = dextromethorphan; NMDA = N-methyl-D-aspartate.

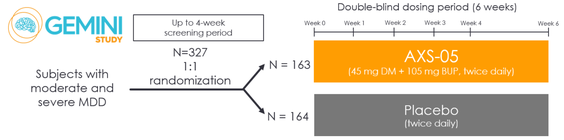
AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:[8,9]

- 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]

Trial Objective and Design

- 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

Primary Endpoint:

- Change from baseline in the MADRS total score at Week 6

Secondary Endpoints:

- **Quality of Life Enjoyment and Satisfaction Questionnaire Short Form[6,10]** The **Q-LES-Q-SF** is a 16-item self-report questionnaire designed to assess the degree of enjoyment and satisfaction experienced by subjects in various aspects of daily functioning. The first 14 items are scored by patients on a 5-point scale ranging from 1 (Very Poor) to 5 (Very Good), and evaluate satisfaction or enjoyment related to physical health, medications, feelings, work/school and household duties, leisure-time activities, social relations, and general activities. The total raw score is reported as percentage of maximum possible score, with higher percentages indicating better QoL
- **Sheehan Disability Scale[6]** The **SDS** is a self-rated questionnaire that evaluates functional impairment across 3 domains: work/school, social life, and family life/home responsibility. Patients rate their degree of impairment from 0 (none) to 10 (extreme) across these domains. Total scores range from 0-30 with higher scores indicating greater impairment

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 :

- 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

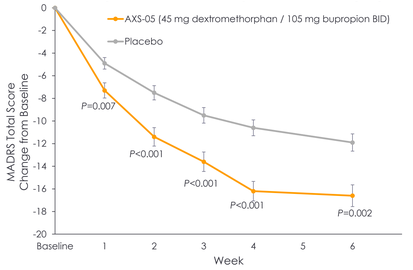
	AXS-05 N = 156	Placebo N=162
Age (years)	42.1 (12.8)	41.1 (13.8)
Female gender, n (%)	95 (60.9%)	117 (72.2%)
Race, n (%)		
White	84 (53.8%)	92 (56.8%)
Black or African American	58 (37.2%)	54 (33.3%)
BMI (mg/kg²)	29.3 (5.61)	29.3 (5.69)
MADRS total score	33.6 (4.43)	33.2 (4.36)
SDS total score	20.3 (5.96	19.3 (5.82)
Q-LES-Q-SF total score (% maximum)	34 (13.46)	36 (12.29)

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

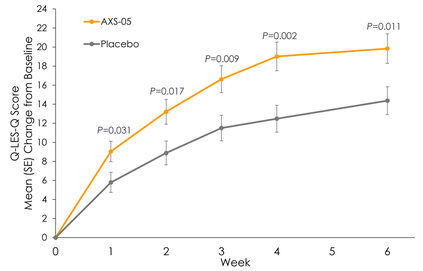
Results

Rapid and Robust Improvement in Symptoms of Depression



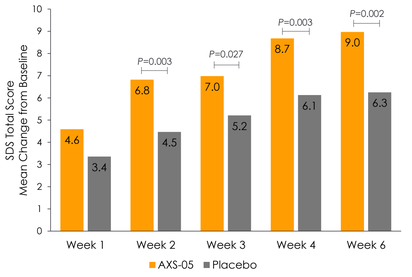
- AXS-05 achieved the primary endpoint – statistically significant reduction from baseline on the MADRS total score at week 6 (-16.6 vs. -11.9, p=0.002), compared to placebo
- AXS-05 rapidly and statistically significantly reduced MADRS total score compared to placebo by week 1 (-7.3 vs. -4.9, p=0.007), the first timepoint measured, and at all timepoints thereafter

Rapid and Sustained Improvement in Quality of Life



- AXS-05 rapidly and statistically significantly improved QoL as early as Week 1 (p=0.031), the first timepoint assessed, as compared to placebo
- Over 6 weeks of treatment, AXS-05 demonstrated increasing levels of QoL improvements compared to placebo, with statistical significance at all timepoints

Rapid and Sustained Improvement in Functioning



- AXS-05 rapidly improved functioning on the SDS total score with statistical significance by Week 2 (p=0.003) compared to placebo
- AXS-05 demonstrated durable and statistically significant functional improvements from Week 2 onwards compared to placebo

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

- AXS-05 was generally safe and well tolerated
- The 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
- AXS-05 was not associated with psychotomimetic effects, increased sexual dysfunction, or weight gain

Conclusions

- **AXS-05 treatment resulted in rapid, substantial and sustained improvements in QoL and functioning, in tandem with antidepressant effects, in patients with MDD**
- **Statistically significant improvements in MADRS and Q-LES-Q-SF scores were demonstrated with AXS-05, as early as Week 1 and sustained to Week 6, compared to placebo**
- **Treatment with AXS-05 resulted in statistically significant improvements in functioning, on the SDS, as early as Week 2 and sustained to Week 6, as compared to placebo**
- **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**
- **These findings suggest that AXS-05, a mechanistically novel, oral, NMDA receptor antagonist with multimodal activity, rapidly improves depressive symptoms, quality of life, and functioning in patients with MDD**

References

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Disclosures: COG, AJ, ZT, and HT are employees of Axsome Therapeutics.