Sustained Efficacy with Long-term Treatment with AXS-05: Results from the COMET Phase 3 Trial, a Long-term, Open-label Study Evaluating the Efficacy and Safety of AXS-05 for the Treatment of MDD

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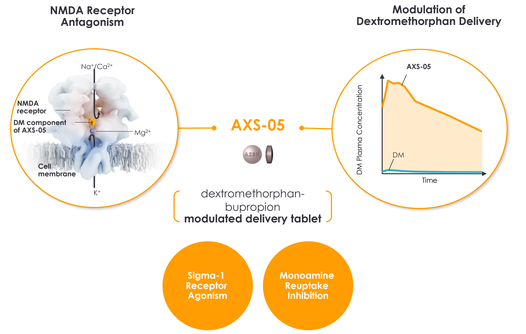
Introduction

- **Major depressive disorder (MDD) is a serious illness:** 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 antidepressants (STAR*D trial results), and the majority of these patients also fail second-line treatment (69%)[3]
- **Need for mechanistically novel approaches:** Currently approved oral antidepressants act primarily via monoaminergic mechanisms[4] and are associated with prolonged time to clinically meaningful response (up to 6-8 weeks)[3] and adverse events that can impact adherence to treatment[5]
- **There is therefore an urgent need for:** Mechanistically-novel, effective, well-tolerated and rapidly-acting antidepressants that can provide sustained clinical benefit[6]

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.** Machado-Vieira R, et al. Prog Neurobiol. 2017;152:21-37. **5.** Ginsberg LD. CNS Spectrums. 2009;14: 8–14. **6.** Baldessarini RJ, et al. Psychother Psychosom. 2017;86:65–72. **7.** Stahl SM. CNS Spectr. 2019 Oct;24(5):461-466.

Trial Objective

- The objective of the COMET Phase 3 trial was to evaluate the long-term efficacy and safety of AXS-05 in the treatment of major depressive disorder

Trial Design

- The COMET trial was a Phase 3, multi-center, open-label U.S. trial
- Subjects were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion) twice daily for up to 12 months
- This study enrolled both subjects completing a prior AXS-05 study and newly enrolled subjects
- A total of 876 subjects were treated with AXS-05, including 611 newly enrolled subjects
- Here we present the efficacy results of the newly enrolled subjects (n=611) and the safety results from the full population (n=876)

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

Key exclusion criteria:

- History of ECT, vagus nerve stimulation, TMS or experimental CNS treatment during the current episode or within 6 months
- Schizophrenia, bipolar disorder, obsessive compulsive disorder
- Psychiatric symptoms secondary to any other general medical condition

Efficacy Outcome Measures:

- Montgomery–Åsberg Depression Rating Scale (MADRS)
  - Clinical Response (≥ 50% reduction in MADRS total score)
  - Clinical Remission (≤ 10 on the MADRS total score)
- Clinical Global Impression of Improvement (CGI-I)
- Sheehan Disability Scale (SDS)
  - Clinical Response in Functioning (≤ 12 on the SDS total score)

Baseline Demographics and Clinical Characteristics

	AXS-05
Age, mean (range)	42.4 (18 – 65)
Female sex, n (%)	380 (62.4)
BMI, mean (SD)	31.4 (7.50)
Race, n (%)	
White	354 (58.1)
Black	217 (35.6)
Asian	12 (2.0)
MADRS total score, mean (SD)	32.7 (4.64)
SDS total score, mean (SD)	20.0 (5.78)

BMI = body mass index; MADRS = Montgomery-Asberg Depression Rating Scale; SDS = Sheehan Disability Scale

Safety and Tolerability

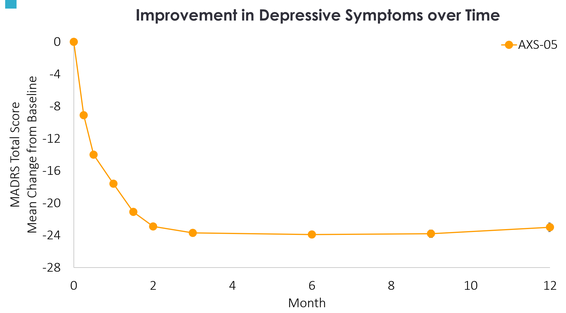
- AXS-05 was generally safe and well-tolerated in the study
- The most commonly reported adverse events (AEs) were dizziness, nausea, headache, dry mouth, and decreased appetite
- Rates of discontinuation due to AEs were low (8.4%)
- The most common AEs resulting in discontinuation were dizziness (1.3%), nausea (1.1%), and headache (1.0%)

Adverse Events Occurring in ≥5% of Subjects

Adverse Event	AXS-05 N (%)
Dizziness	111 (12.7)
Nausea	104 (11.9)
Headache	77 (8.8)
Dry mouth	62 (7.1)
Decreased appetite	53 (6.1)

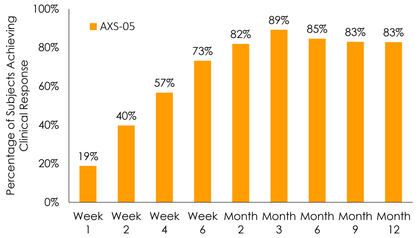
Efficacy Results

Improvement in Depressive Symptoms over Time



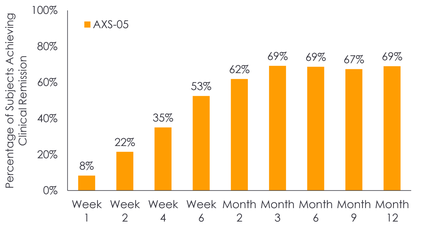
Mean Improvement from Baseline in MADRS Total Score with AXS-05 Treatment					
Week 1	Week 2	Week 4	Week 6	Month 6	Month 12
9.1	14.0	17.6	21.1	23.9	23.0

Clinical Response over Time (≥50% Improvement in MADRS)



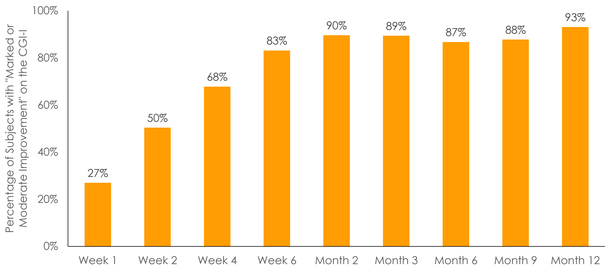
- Clinical response after treatment with AXS-05 was achieved by 18.8% of patients at Week 1, 39.7% of patients at Week 2, and 73.2% of patients at Week 6
- Clinical response after 6 and 12 months of treatment with AXS-05 was achieved by 84.6% and 82.8%, respectively

Clinical Remission over Time (MADRS ≤10)



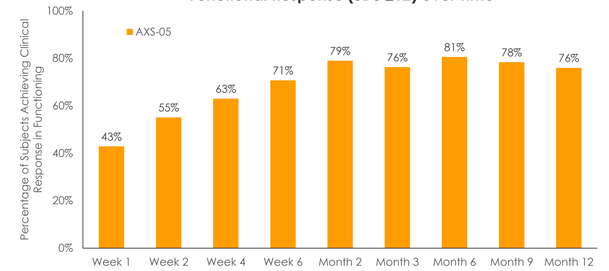
- Clinical Remission after treatment with AXS-05 was achieved by 8.3% of patients at Week 1, 21.5% of patients at Week 2, and 52.5% of patients at Week 6
- Clinical Remission after 6 and 12 months of treatment with AXS-05 was achieved by 68.7% and 69.0% of patients, respectively

Clinician-Reported Global Improvement over Time



- Marked or moderate improvement in depressive symptoms after treatment with AXS-05, assessed by the CGI-I scale, was achieved by 27.0% of patients at Week 1, 50.4% of patients at Week 2, and 83.1% of patients at Week 6
- Marked or moderate improvement after 6 and 12 months of treatment with AXS-05 was achieved by 86.7% and 93.1% of patients, respectively

Functional Response (SDS ≤12) over Time



- The Sheehan Disability Scale (SDS) is a patient-rated scale that assesses functioning in work/school, social life, and family life/home responsibility
- Clinical response on the SDS, after treatment with AXS-05, was achieved by 42.9% of patients at Week 1, 55.1% of patients at Week 2, and 70.7% of patients at Week 6
- Clinical response on the SDS after 6 and 12 months of treatment with AXS-05 was achieved by 80.6% and 75.9% of patients, respectively

Conclusions

- **AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, representing a mechanistically novel approach for the treatment of major depressive disorder**
- **AXS-05 resulted in rapid and substantial reduction in symptoms of depression and improvement in functioning, which were durable over 12 months of treatment**
- **Rates of clinical response and remission on the MADRS, and functional response on the SDS were substantial**
- **AXS-05 was generally safe and well-tolerated in this trial. The most commonly reported adverse events were dizziness, nausea, and headache**

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