Rapid Reduction in Suicidal Ideation in Patients Treated with AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity: Results from the COMET-SI Trial

Cedric O'Gorman, Amanda Jones, Herriot Tabuteau

Axsome Therapeutics, New York, New York

AXSOME THERAPEUTICS

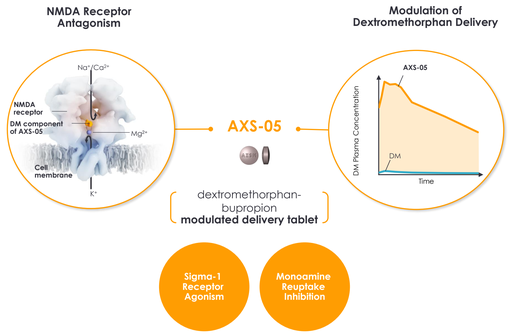
22 Cortlandt Street, 16th Floor, New York, NY 10007

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

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]
- **Suicidal ideation is a major risk factor for suicide in patients with MDD[6,7]**
- **The time between the onset of suicidal ideation and suicide attempt is often very short[8],** highlighting the need for the development of novel rapidly-acting antidepressant treatments
- **There is therefore an urgent need for:** Mechanistically-novel, effective, well-tolerated and rapidly-acting antidepressants that can provide sustained clinical benefit[9]

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:[1,10]

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist[10]
- 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[10]

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.** Bickley H, et al. (2013) Psychiatr Serv 64, pp. 653–659. **7.** McAuliffe CM. (2002) Arch Suicide Res 6, pp. 325–338. **8.** Deisenhammer EA, et al. (2020) J Clin Psychiatry 70, pp. 19–24. **9.** Baldessarini RJ, et al. Psychother Psychosom. 2017;86:65–72. **10.** Stahl SM. CNS Spectr. 2019 Oct;24(5):461-466.

Trial Objective

- The objective of the COMET-SI trial was to evaluate the efficacy and safety of open-label AXS-05 treatment in MDD patients with suicidal ideation (SI)

Trial Design

- COMET-SI was a substudy (n=37) of the COMET (Clinical Outcomes with NMDA-based Depression Treatment) Phase 3, open-label trial (N=876) that evaluated the long-term efficacy and safety of AXS-05
- The COMET study enrolled both subjects completing a prior AXS-05 study and newly enrolled subjects
- Subjects were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion) twice daily for up to 12 months
- The COMET-SI trial evaluated those patients who had suicidal ideation, defined as a score of ≥3 on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI), at baseline

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
- MADRS-SI score ≥ 3

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:

- MADRS-SI Score
- Resolution of Suicidal Ideation (≤ 1 on the MADRS-SI)
- 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 (COMET-SI)

	AXS-05 (N=37)
Age, mean (range)	31.7 (18-63)
Female sex, n (%)	25 (67.6)
BMI, mean (SD)	28.1 (6.90)
Race, n (%)	
White	24 (64.9)
Black	8 (21.6)
Asian	5 (13.5)
MADRS-SI score, mean (SD)	3.4 (0.50)
MADRS total score, mean (SD)	36.8 (4.50)
SDS total score, mean (SD)	21.2 (4.75)

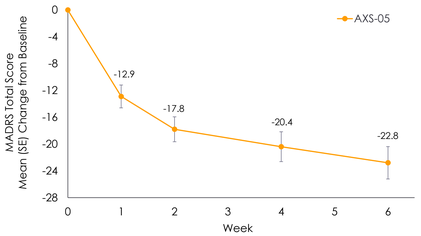
BMI = body mass index; MADRS = Montgomery-Asberg Depression Rating Scale; SDS = Sheehan Disability Scale

Efficacy Results

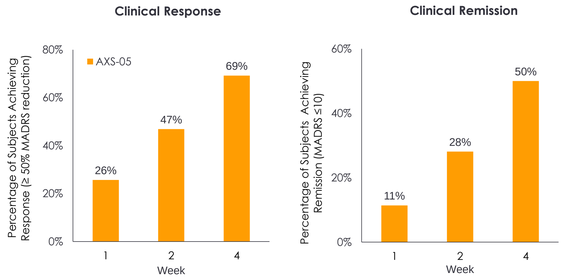
Reduction and Resolution of Suicidal Ideation

- Treatment with AXS-05 was associated with an approximately 70% reduction from baseline in the MADRS-SI score by Week 1, increasing to more than 80% by Week 4
- Resolution of suicidal ideation (MADRS-SI ≤1), after treatment with AXS-05, was achieved by Week 1 in the majority of patients (60.0%), and in nearly 80% of patients by Week 4

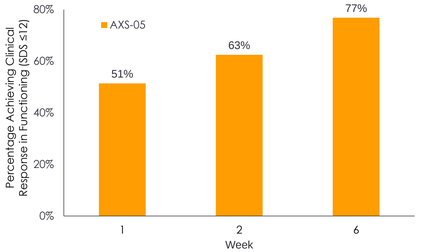
Improvement in MADRS Total Score



Rates of Clinical Response and Remission



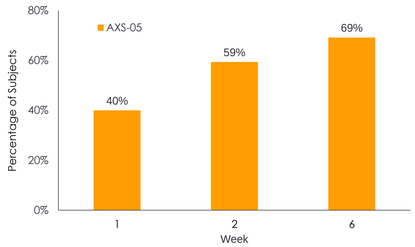
Response Rates in Functioning



- The Sheehan Disability Scale (SDS) is a patient-rated scale that assesses functioning in work/school, social life, and family life/home responsibility
- Functional response on the Sheehan Disability Scale (defined as a total score of ≤12), after treatment with AXS-05, was achieved by 51.4% of patients at Week 1, 62.5% of patients at Week 2, and 76.9% of patients at Week 6

Clinician-Reported Global Improvement

Proportion of Patients with Marked or Moderate Improvement



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 MDD**
- **The COMET-SI substudy evaluated the effect of open-label treatment with AXS-05 in reducing and resolving suicidal ideation, and improving depressive symptoms and functioning in MDD patients with suicidal ideation**
- **MDD patients with suicidal ideation, when treated with AXS-05, experienced rapid resolution of suicidal ideation, and improvement in overall depressive symptoms and functioning**
- **AXS-05 was generally safe and well-tolerated in this trial. The most commonly reported adverse events were dizziness, nausea, and headache**