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Sustained Effects of AXS-05, an Oral NMDA Receptor Antagonist, in Treatment Resistant Depression Patients: Results from the COMET-TRD Trial

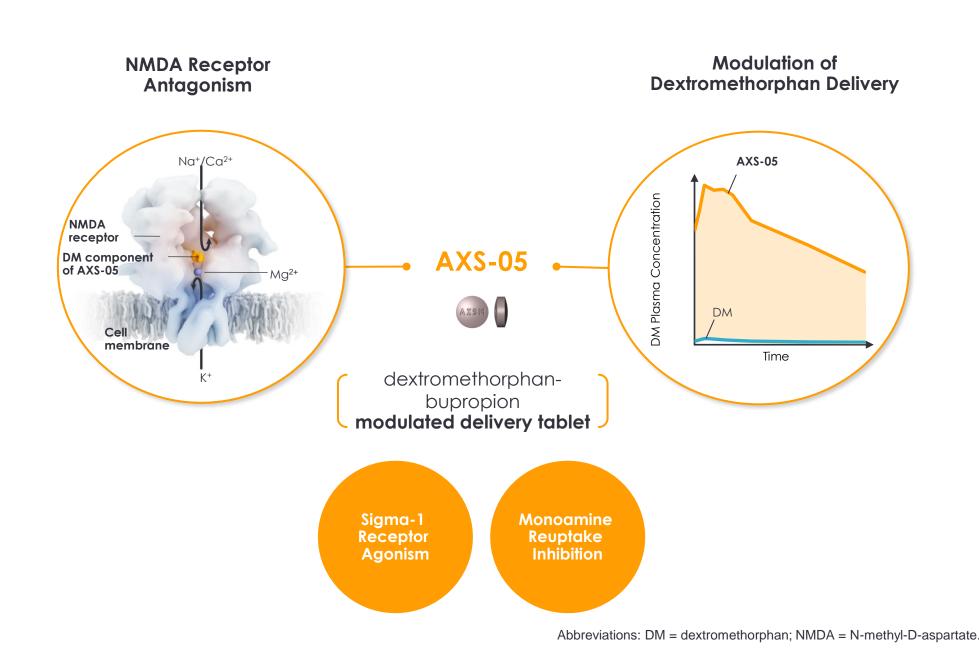
Amanda Jones, Cedric O'Gorman, Herriot Tabuteau

Axsome Therapeutics, New York, New York

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 mechanisms⁴ and are associated with prolonged time to clinically meaningful response (up to 6-8 weeks)³ and adverse events that can impact adherence to treatment⁵
- There is therefore an urgent need for: Mechanistically-novel, effective, well-tolerated and rapidly-acting antidepressants that can provide sustained clinical benefit⁶

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



AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:^{1,7}

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist⁷
- 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 inhibitor⁷

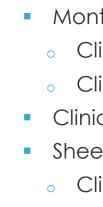
References

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.

- COMET-TRD was a substudy (n=70) 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 as well as newly enrolled subjects

- DSM-5 criteria for current MDD without psychotic features at Enrollment Baseline
- Use of 2 or more prior ADT(s) within the current major depressive episode, prior to receiving AXS-05

Efficacy Outcome Measures:





Trial Objective

• The objective of the COMET-TRD trial was to evaluate the long-term efficacy of open-label AXS-05 treatment in patients with treatment resistant depression (TRD)

Trial Design

- COMET-TRD evaluated those patients with ongoing depressive symptoms despite treatment with 2 or more antidepressants (ADTs) in the current depressive episode
- Subjects were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion) twice daily for up to 12 months

Key inclusion criteria:

- Male or female 18-65 years of age
- MADRS total score of ≥ 25

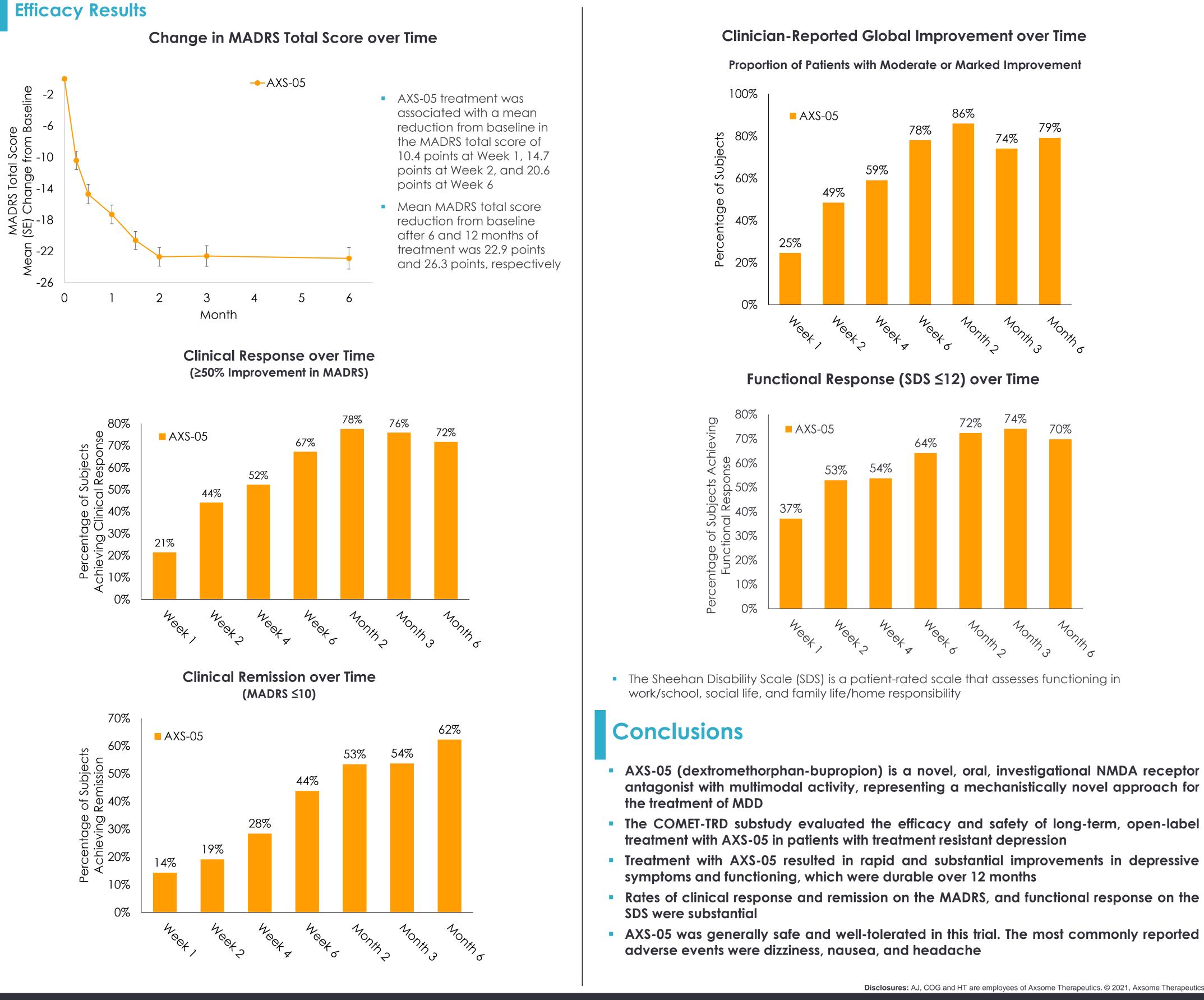
Key exclusion criteria:

- 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
- Montgomery–Åsberg Depression Rating Scale (MADRS)
 - Clinical Response (\geq 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 (N=70)
Age, mean (range)	43.8 (18 – 65)
Female sex, n (%)	51 (72.9%)
BMI, mean (SD)	31.4 (7.50)
Race, n (%)	
White	44(62.9%)
Black	21 (30.0%)
Prior ADTs, mean (SD)	2.8 (1.29)
MADRS total score, mean (SD)	33.1 (4.10)
SDS total score, mean (SD)	19.0 (6.49)

BMI = body mass index; ADT=Antidepressant Treatment; MADRS = Montgomery-Asberg Depression Rating Scale; SD = standard deviation; SDS = Sheehan Disability Scale





22 Cortlandt Street, 16th Floor, New York, NY 10007 For more information, please contact Cedric O'Gorman at **cogorman@axsome.com**