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AXS-05 (Dextromethorphan-Bupropion) Significantly Improved Functioning in Major Depressive Disorder: Analysis of the Domains of the Sheehan Disability Scale

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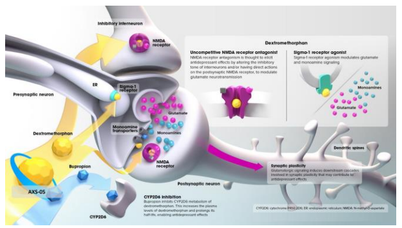
Introduction

- Major depressive disorder (MDD) is the leading cause of disability worldwide[1]
- American Psychiatric Association guidelines recognize the importance of maximizing the individual's level of functioning as a goal of treatment,[2] and individuals with MDD rate a return to usual functioning as a very important outcome of treatment[3]
- Certain depressive symptoms impair function more than others, and individual symptoms impact functional domains to differing degrees; sad mood, concentration, fatigue, and loss of interest account for much of the known variance in impairment related to MDD[4]
- Workplace costs, which include absenteeism and presenteeism, contributed 61% of the total MDD economic burden in 2018[5]
- Improvement in functioning generally lags behind symptomatic improvement,[6,7] and the asynchrony between symptomatic and functional improvement continues to be an unmet need for patients with MDD[7]
- Residual functional impairment is associated with an increased risk of relapse of MDD[6]
- The Sheehan Disability Scale (SDS)[8] is a well-validated, short, patient-report scale assessing functional impairment in work or school, social life and leisure activities, and family life and home responsibilities
  - Total scores range from 0–30, with higher scores indicating more severe impairment
  - Each domain is rated 0–10

AXS-05: An Oral, NMDA Receptor Antagonist With Multimodal Activity[9,10]



- In a pooled analysis of controlled studies, AXS-05 demonstrated rapid improvements in the majority of Montgomery-Åsberg Depression Rating Scale (MADRS) items, including those that are associated with functional impairment[11]

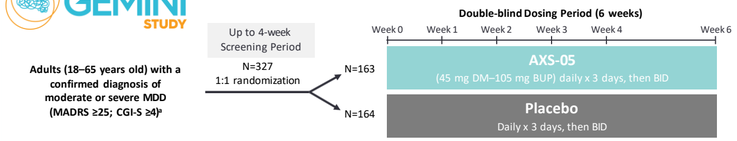
Objective

- To explore the effects of AXS-05 on daily function, these post hoc analyses evaluated functional disability assessed by the SDS domain scores over 6 and 52 weeks in two phase 3 studies in MDD

GEMINI Study

Methods

GEMINI Study Design[12]



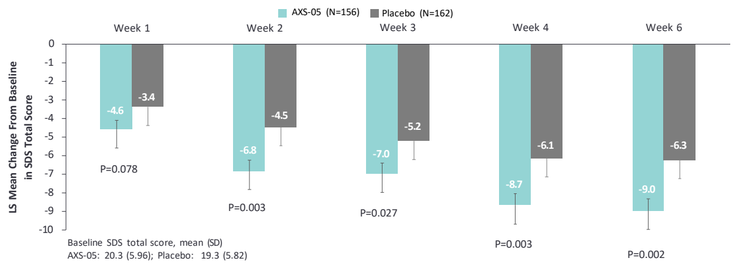
[a]Exclusion criteria (not exhaustive): treatment-resistant MDD, comorbid psychiatric conditions, significant risk of suicide, seizure disorder, and concomitant psychotropic medications. BID, twice daily; BUP, bupropion; CGI-S, Clinical Global Impression-Severity; DM, dextromethorphan, MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder.

- Post hoc analysis of change from baseline SDS total and individual domain scores
- MMRM analysis; mITT population (missing data not imputed)

Results

- In the AXS-05 and placebo groups, respectively, mean age was 42 and 41 years, 61% and 72% were female, mean MADRS total score was 33.6 and 33.2, and mean Clinical Global Impression-Severity score was 4.6 and 4.6

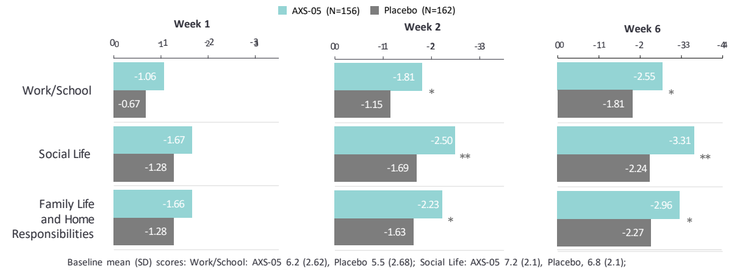
SDS Total Score Improvement: GEMINI



Baseline SDS total score, mean (SD)
AXS-05: 20.3 (5.96); Placebo: 19.3 (5.82)

All P values are nominal. LS, least squares; SDS, Sheehan Disability Scale.

SDS Domain Scores Improvement: GEMINI



Baseline mean (SD) scores: Work/School: AXS-05 6.2 (2.62), Placebo 5.5 (2.68); Social Life: AXS-05 7.2 (2.1), Placebo, 6.8 (2.1); Family Life and Home Responsibilities: AXS-05 6.7 (2.4), Placebo, 6.7 (2.4).

Values shown represent LS mean change from baseline. *Nominal P<0.05 **Nominal P<0.01.

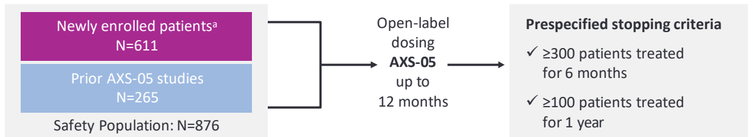
Improvement in Underproductive Days: GEMINI Study

- At baseline, patients in the AXS-05 and placebo groups were underproductive 4.2 and 4.0 days per week, respectively; at Week 6, the least squares mean change was −2.1 days (52% improvement) and −1.7 days (40% improvement), respectively (P=0.075)

COMET Study

Methods

COMET Study Design[13,14]



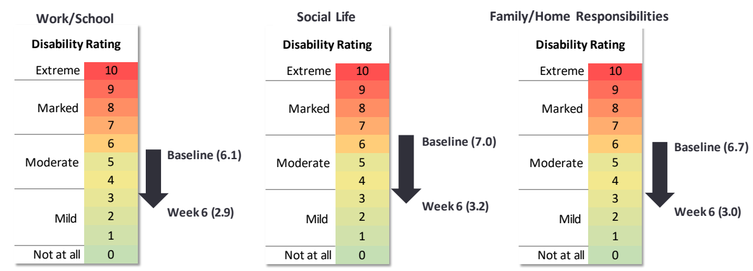
[a]Inclusion criteria (not exhaustive): adults (18–65 years old), diagnosis of MDD, and MADRS score ≥25. Exclusion criteria (not exhaustive): comorbid psychiatric conditions, seizure disorder, and prohibited treatments prior to enrollment. MADRS, Montgomery-Åsberg Depression Rating Scale.

- Post hoc analysis of change from baseline in SDS total and individual domain scores
- Descriptive statistics; mITT population (missing data not imputed)

Results

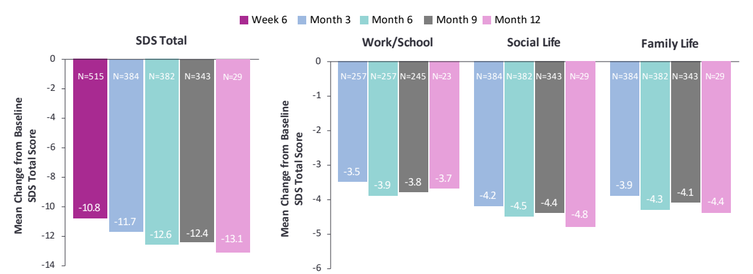
- Among all participants, mean age was 42.5 years, 64% were female, and 58% were white; among newly enrolled patients, mean MADRS total score was 32.7 and mean SDS total score was 20.0

Improvement in SDS Domains at Week 6: COMET Study



SDS, Sheehan Disability Scale.

SDS Summary: COMET Long-term Results



SDS, Sheehan Disability Scale.

Improvement in Underproductive Days: COMET Study

Time point	Baseline	Week 6	Month 3	Month 9	Month 12
Underproductive days per week	4.0	1.4	1.1	1.0	0.7

- At Week 6 of AXS-05 treatment, there was a 65% improvement in underproductive days

Safety and Tolerability

- In **GEMINI**, the most common adverse reactions in AXS-05–treated individuals (≥5% and twice the rate of placebo) were: dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%)
  - Additional AEs occurring in ≥2% of AXS-05–treated individuals and more frequently than in placebo-treated individuals were nausea, anxiety, constipation, decreased appetite, insomnia, arthralgia, fatigue, paresthesia, and vision blurred
- In **COMET**, AEs reported in ≥5% of AXS-05–treated individuals were dizziness (12.7%), nausea (11.9%), headache (8.8%), dry mouth (7.1%), and decreased appetite (6.1%)

Conclusions

- Treatment with AXS-05 improved SDS total scores starting at Week 2, coinciding with early improvements in depressive symptoms
- AXS-05 improved functional disability in the SDS domains of Work/School, Social Life, and Family Life/Home Responsibilities in people with MDD in both GEMINI and COMET
- Improvements were demonstrated in number of underproductive days, which is a key contributor to the economic burden of MDD
- AXS-05 treatment was generally well tolerated in both short- and long-term studies

References: 1. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. **2.** Gelenberg A., et al. (2010). American psychiatric association practice guidelines for the treatment of patients with major depressive disorder. Am. J. Psychiatry 167 (Suppl. 10), 9–110. **3.** Zimmerman M, et al. *Am J Psychiatry*. 2006;163:148-50. **4.** Fried EI, Nesse RM. *PLoS One*. 2014;9:e90311. **5.** Greenberg PE, et al. *Pharmacoeconomics*. 2021;39:653-665. **6.** Cutler AJ, et al. *Prim Care Companion CNS Disord*. 2015;17:10.4088/PCC.14m01753. **7.** Sheehan DV, et al. *J Affect Disord*. 2017;215:299-313. **8.** Sheehan KH, Sheehan DV. *Int Clin Psychopharmacol*. 2008;23:70-83. **9.** Stahl SM. *CNS Spectr*. 2019;24:461-466. doi: 10.1017/S1092852919001470. Erratum in: *CNS Spectr*. 2020;25:803. **10.** AUVELITY® [full prescribing information]. New York, NY: Axsome Therapeutics, Inc. **11.** Jones A, et al. *CNS Spectr*. 2023;28:263. **12.** Iosifescu DV, et al. *J Clin Psychiatry*. 2022;83:21m14345. **13.** O'Gorman C, et al. Presented at: American Society of Clinical Psychopharmacology Annual Meeting June 2021. **14.** Data on file. Axsome Therapeutics.

Disclosures: A Cutler is a consultant to Axsome. All other authors are current or former employees of Axsome.