Evaluation of AXS-05 (dextromethorphan-bupropion) in Major Depressive Disorder Using the Interest-Activity Domain

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Key Questions

- Does AXS-05 improve interest-activity symptoms in people with MDD?
- Does severity of interest-activity symptoms at baseline impact depression outcomes with AXS-05 treatment?

Conclusions

- In people with MDD, prominent interest-activity symptoms (low interest, reduced activity, indecisiveness, and lack of enjoyment) at baseline are associated with poor treatment response to serotonergic antidepressants
- This post hoc analysis evaluated the interest-activity symptom score, a newer measure derived from the MADRS and QIDS-SR
- AXS-05, an oral NMDA receptor antagonist and sigma-1 receptor agonist, significantly improved interest-activity symptom scores compared with control
- AXS-05 exhibited comparable reductions in depressive symptoms regardless of severity of baseline interest-activity symptoms
- These results suggest that AXS-05 may be a particularly effective treatment option in individuals with MDD who have substantially impaired interest and activity

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Z Thomas, G Eglit, C Andersson, S Somkuwar, and H Tabuteau are employees of Axsome Therapeutics.

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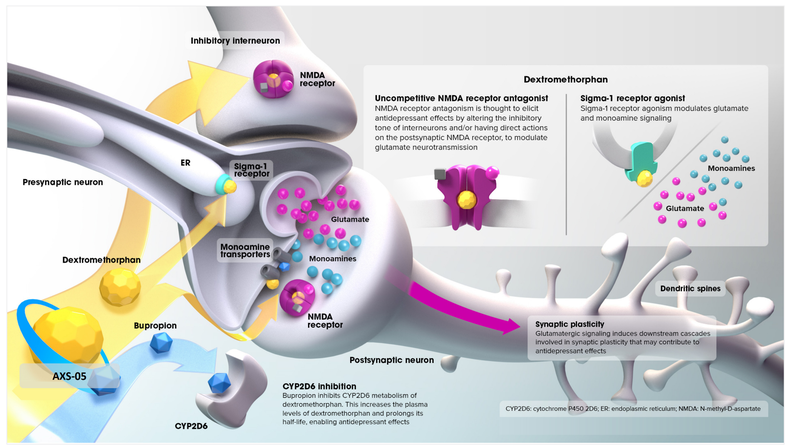
Introduction

- Major depressive disorder (MDD) is a highly prevalent, chronic, disabling disorder and a leading cause of suicide[1]
- In people who respond to monoaminergic antidepressants, it often takes weeks to observe clinically meaningful improvements in depression symptoms[2]
- Serotonergic antidepressants have demonstrated reduced effectiveness in people with depression who have prominent symptoms of impaired interest and activity (low interest, reduced activity, indecisiveness, and lack of enjoyment), a finding that has been replicated in multiple studies, including:
  - Genome-based Therapeutic Drugs for Depression (GENDEP; N=811)[3]
  - Sequenced Treatment Alternatives to Relieve Depression (STAR*D; a subgroup of N=3637)[3]
  - Canadian Biomarker Integration Network in Depression trial 1 (CAN-BIND-1; N=211)[4]
- Therefore, alternative, mechanistically novel antidepressants are needed for individuals with MDD who have impairments in interest and activity

AXS-05: A Novel, Oral NMDA Receptor Antagonist

- AXS-05 (dextromethorphan-bupropion [Auvelity® extended-release tablet]) is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist approved by the US Food and Drug Administration for the treatment of MDD in adults (**Figure 1**)[5]
  - Dextromethorphan is an antagonist of the NMDA receptor and a sigma-1 receptor agonist[5]
  - Bupropion is an aminoketone and cytochrome P450 2D6 inhibitor that increases the bioavailability of dextromethorphan[5]

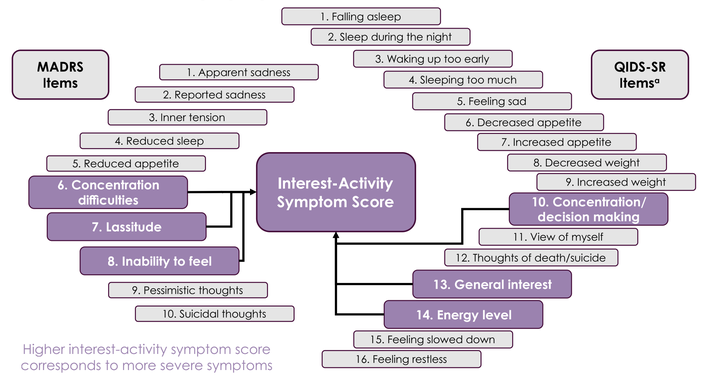
Figure 1. AXS-05 mechanism of action



Methods & Study Design

- This post hoc analysis pooled data from 2 double-blind, randomized, controlled, 6-week trials of AXS-05 in individuals with moderate to severe MDD
  - The GEMINI trial (NCT04019704) was placebo controlled (AXS-05, n=156; placebo, n=162)[6]
  - The ASCEND trial (NCT03595579) used bupropion as an active control (AXS-05, n=43; bupropion, n=37)[7]
- Both studies met their primary endpoint, with AXS-05 demonstrating statistically significant improvement on the Montgomery Åsberg Depression Rating Scale (MADRS) compared with control[6,7]
- This analysis investigated the interest-activity symptom score, which has been used previously[4] and is defined by the sum of 3 MADRS items (concentration, lassitude, and inability to feel) and 3 Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) items (concentration, interest, and energy) (**Figure 2**)[4]

Figure 2. Interest-activity symptom score components



[a] As reported previously,[4] the QIDS-SR items (with scores from 0 to 3) were doubled for equal weight with the MADRS items (with scores from 0 to 6).
MADRS, Montgomery Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.

- This post hoc pooled analysis evaluated 2 hypotheses (**Table 1**)

Table 1. Study hypotheses and statistical methods

Hypothesis	Statistical method
1. AXS-05 would produce greater improvement in interest-activity change from baseline compared with control	MMRM using unstructured variance-covariance structure was fit with change from baseline in interest-activity. Fixed effects consisted of baseline interest-activity score, treatment group, week, and the interaction of treatment group and week. Treatment effects (differences from placebo) were estimated based on estimated marginal means at each treatment week and overall by marginalizing across treatment weeks. Responder analyses conducted evaluating probabilities of achieving ≥50% reduction from baseline in interest-activity scores with Chi square tests
2. Efficacy of AXS-05 would be maintained regardless of individuals' baseline severity of interest-activity score	MMRM assuming an unstructured variance-covariance structure was fit with MADRS change from baseline as the outcome. Fixed effects consisted of baseline MADRS score, treatment group, week, baseline interest-activity score, treatment group x week, treatment group x baseline interest-activity score, week x baseline interest-activity score, and the 3-way interaction between treatment group, week, and baseline interest-activity score. Simple slopes were evaluated

MADRS, Montgomery Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures.

Key Findings

Patient Population

- Baseline demographics and clinical characteristics were similar between groups (**Table 2**)

Table 2. Baseline demographics and characteristics

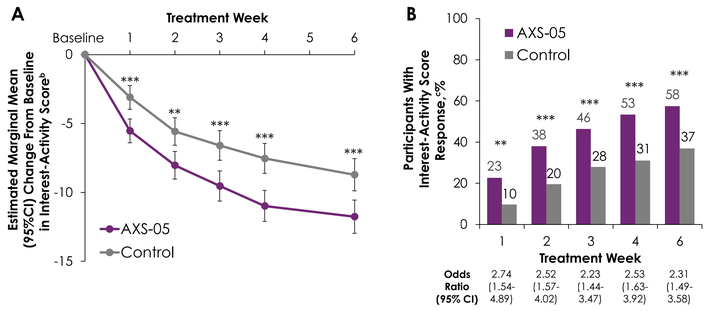
	AXS-05 (n=199)	Control (n=199)
Age, mean (SD), years	41.0 (12.8)	40.5 (13.5)
Women, n (%)	120 (60)	143 (72)
Race, n (%)[a]		
White	114 (57)	112 (56)
Black	70 (35)	68 (34)
Asian	10 (5)	8 (4)
Other[b]	5 (3)	11 (6)
Prior antidepressant treatment during the current MDE, n (%)[c]		
No prior treatment	155 (78)	135 (68)
Prior treatment	44 (22)	64 (32)
Depression severity, n (%)		
MADRS total score <35	131 (66)	130 (65)
MADRS total score ≥35	68 (34)	69 (35)
MADRS total score, mean (SD)	33.2 (4.40)	32.9 (4.40)
Interest-activity symptom score, mean (SD)	22.6 (4.51)	22.4 (4.77)

[a] May not sum to 100% due to rounding. [b] Includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, multiple races, other, or not reported. [c] Individuals with treatment-resistant depression (defined as having had ≥2 failed adequate antidepressant treatments in the current MDE) were excluded from ASCEND and GEMINI.
MADRS, Montgomery Åsberg Depression Rating Scale; MDE, major depressive episode.

Hypothesis 1. AXS-05 would produce greater improvement in interest-activity compared with control

- AXS-05 treatment significantly improved change from baseline (reduced score) in interest-activity symptom score compared with placebo at every time point (**Figure 3A**)
- A significantly greater percentage of people achieved interest-activity symptom score response with AXS-05 compared with placebo at every time point (**Figure 3B**)

Figure 3. Interest-activity symptom score[a] change from baseline (A) and response (B)

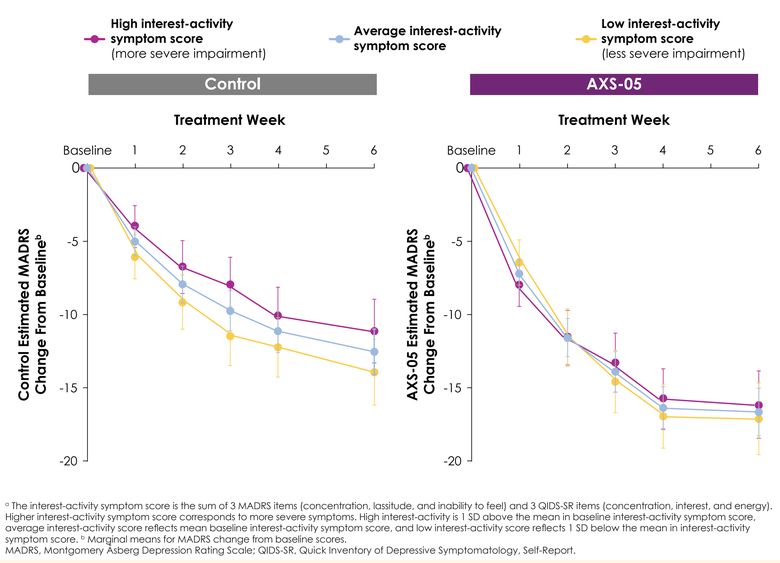


**P<.01, ***P<.001. Not adjusted for multiple comparisons.
[a] The interest-activity symptom score is the sum of 3 MADRS items (concentration, lassitude, and inability to feel) and 3 QIDS-SR items (concentration, interest, and energy). Higher interest-activity symptom score corresponds to more severe symptoms. [b] Estimates derived from MMRM with an unstructured covariance with fixed effects for baseline interest-activity symptom score, week, treatment group, and interaction terms for week and treatment group. [c] Response defined as ≥50% improvement on interest-activity symptom score from baseline.
MADRS, Montgomery Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.

Hypothesis 2. Efficacy of AXS-05 would be maintained regardless of individuals' baseline severity of interest-activity score

- In the control group, higher baseline interest-activity impairment was associated with less improvement in MADRS total score (simple slopes b, 0.27; 95% CI, 0.02 to 0.52; *P*<.05) (**Online Figure**)
- There was no significant association between baseline interest-activity symptom score with MADRS total score in the AXS-05 group (simple slopes b, -0.04; 95% CI, -0.24 to 0.31; *P*=.787)
  - There was no association between baseline interest-activity symptom score and MADRS change from baseline in the AXS-05 group at any treatment week (all *P* values >.05)
- Changes from baseline in MADRS total score were similar among participants with low, average, and high baseline interest-activity symptom scores throughout the trial in the AXS-05 treatment group, but differed in the control treatment group (**Figure 4**)
  - In the control group, high baseline interest-activity symptom scores were associated with less improvement in depression symptoms

Figure 4. Change in MADRS total score by baseline interest-activity symptom score[a]



[a] The interest-activity symptom score is the sum of 3 MADRS items (concentration, lassitude, and inability to feel) and 3 QIDS-SR items (concentration, interest, and energy). Higher interest-activity symptom score corresponds to more severe symptoms. High interest-activity is 1 SD above the mean in baseline interest-activity symptom score, average interest-activity score reflects mean baseline interest-activity symptom score, and low interest-activity score reflects 1 SD below the mean in interest-activity symptom score. [b] Marginal means for MADRS change from baseline scores.
MADRS, Montgomery Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.

Safety

- The most commonly reported adverse reactions (≥5% and twice the rate of placebo) with AXS-05 were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis