Effects of AXS-05 (Dextromethorphan-Bupropion) in Improving Anhedonia and Interest-Activity Symptoms of MDD and the Associated Improvements in Functional Impairment

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Objectives

- To evaluate the efficacy of Auvelity® (AXS-05) on treating anhedonia symptoms and diminished interest-activity in individuals with MDD
- To assess the relationship between anhedonia symptoms and functional impairment in individuals with MDD

Conclusions

- This pooled post hoc analysis showed that AXS-05 compared with controls significantly improved anhedonia and impaired interest-activity symptoms starting as early as Week 1
- AXS-05 exhibited comparable reductions in total MADRS scores regardless of severity of baseline interest-activity symptoms
- Functional improvements with AXS-05 treatment as measured by the SDS were positively correlated with the improvement in anhedonia symptoms in the Phase 3 GEMINI study
- These results suggest AXS-05 may have benefits in reducing anhedonia and improving interest-activity, symptoms of MDD that can be very difficult to resolve with monoaminergic-targeted therapies

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BACKGROUND

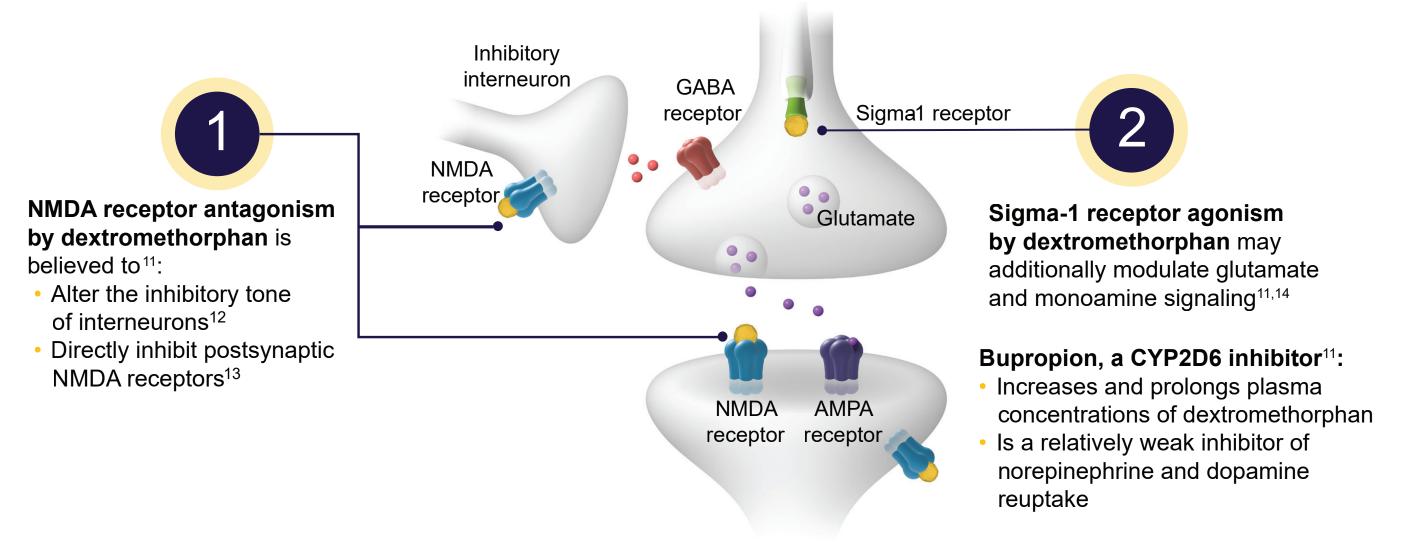
- Major depressive disorder (MDD) is a disabling and prevalent disorder that is a leading cause of suicide in the US^{1,2}
- Anhedonia, or impairments in the motivation/ reward system, including inability to anticipate and/or experience pleasure, is present in up to 75% of individuals diagnosed with MDD³; it is also associated with functional impairment, reduce quality of life, suicidality, and a more chronic
- course of disease^{4,5} Anhedonia can be conceptualized partly as a loss of interest or pleasure in activities (referred to as "interest-activity")6
- Current serotonergic and noradrenergic antidepressants have shown limited efficacy in treating anhedonia and residual anhedonia symptoms are associated with poorer patien
- N-methyl-D-aspartate (NMDA) receptor antagonism has been shown to have antidepressant effects in animal models and clinical trials, establishing the role of glutamatergic
- Clinical evidence suggests that glutamatergic modulation can be effective at improving measures of anhedonia in patients with MDD¹⁰
- There is an urgent clinical need for new treatment improve functional impairment associated with MDD

RESULTS

Study population

dysfunction in the pathogenesis of depression8,

Figure 1. AXS-05 Mechanism of Action



AXS-05

Auvelity® (AXS-05) (45-mg dextromethorphan/105-mg bupropion) is a novel, oral NMDA receptor antagonist, sigma-1 receptor agonist, and aminoketone CYP2D6 inhibitor (Figure 1)¹³

agonism is also associated with anti-inflammatory and neuroprotective activity

- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist that modulates monoamine and glutamate neurotransmission; sigma-1
- The bupropion component of AXS-05 is an aminoketone and a CYP2D6 inhibitor that serves to increase the

METHODS

Study design

- This was a pooled post hoc analysis of data from two double-blind, randomized, controlled, 6-week trials of AXS-05 in adult participants (age 18-65 years) with moderate to severe MDD (defined as a score of ≥25 on the Montgomery-Åsberg Depression Rating Scale [MADRS] and a score of ≥4 on the Clinical Global Impressions severity scale [CGI-S])
- GEMINI (NCT04019704) was a phase 3, placebo-controlled study (modified intent-to-treat population: AXS-05 n=156; placebo, n=162)¹⁷
- ASCEND (NCT03595579) was a phase 2 study that used bupropion as an active control (efficacy population) AXS-05, n=43; bupropion, n=37)¹⁸
- In this analysis, data from the AXS-05 arms were pooled, and the active control and placebo arm were pooled

Post hoc analyses

Anhedonia symptoms were evaluated using the MADRS Anhedonia subscale (Items 1, 2, 6, 7, 8) and the Interest-Activity scale (MADRS Items 6, 7, 8 and Quick Inventory of Depressive Symptomatology Self Report [QIDS-SR] Items 10, 13, 14) (**Figure 2**)

Key analyses

- Least square mean difference (LSMD) from baseline in the MADRS anhedonia sub score and interestactivity score
- Percentage of responders (participants achieving ≥50% reduction) in MADRS anhedonia sub score and Interest-Activity symptom score
- LSMD from control on the MADRS total score at low (1 SD below the mean; less severe impairment) average, and high (1 SD above the mean; more severe impairment) baseline interest activity scores
- Correlation between improvements in the MADRS anhedonia subscale and SDS (Sheehan Disability

Figure 2. MADRS Anhedonia Sub Score (A) and Interest-Activity Symptom Score from MADRS and QIDS-SR (B)

9. Pessimistic thoughts

10. Suicidal thoughts

B. Interest-Activity Symptom Score from MADRS and QIDS-SR A. MADRS Anhedonia Sub Score 1. Falling asleep **MADRS Items** 2. Sleep during the night 3. Waking up too early QIDS-SR MADRS Apparent sadness 4. Sleeping too much 2. Reported sadness 3. Inner tension 6. Decreased appetite 4. Reduced sleep 7. Increased appetite 5. Reduced appetite 8. Decreased weight Interest - Activity 9. Increased weigh difficulties 3. Inner tension 8. Inability to feel decision making 11. View of myself

8. Inability to feel

9. Pessimistic thoughts

10. Suicidal thoughts

4. Reduced sleep

5. Reduced appetite



Table 1. Baseline Demographics and Clinical Characteristics (ASCEND/GEMINI)

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Parameter	AXS-05 (n=199)	Control ^a (n=199)			
Age, median (range), y	41 (18-64)	39 (18-65)			
Women, n (%)	120 (60)	143 (72)			
Race, n (%)					
White	114 (57)	112 (56)			
Black or African American	70 (35)	68 (34)			
Asian	10 (5)	8 (4)			
Other	5 (3)	11 (6)			
BMI, median (range), kg/m²	29.1 (18.2-39.8)	29.6 (18.1-39.7)b			
Prior ADT during index MDE, n (%)					
No prior ADT	155 (78)	135 (68)			
Prior ADT	44 (22)	64 (32)			
Baseline MADRS Total score, mean (SD)	33.2 (4.4)	32.9 (4.4)			
Baseline MADRS Anhedonia score, mean (SD) ^c	19.5 (2.6)	19.5 (2.4)			
Baseline Interest-Activity score, mean (SD)d	22.6 (4.5)	22.4 (4.8)			
CGI-S score, mean (SD)	4.6 (0.6)	4.6 (0.6)			
SDS score, mean (SD) ^e	20.3 (6.0)	19.3 (5.8)			

^aASCEND, bupropion; GEMINI, placebo. ^bn=198. ^cMaximum MADRS anhedonia score is 30. ^dMaximum Interest-Activity score is 36. ^eGEMINI only ADT, antidepressant treatment; BMI, body mass index; CGI-S, Clinical Global Impressions severity scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; SDS, Sheehan Disability Scale.

The pooled baseline demographics and clinical characteristics from GEMINI and ASCEND were similar between AXS-05 and control arms (Table 1)

MADRS anhedonia subscale and SDS correlation (GEMINI only)

Table 2. Within-Subject Correlation Between SDS and MADRS

	Anhedonia Score over the 6-week GEMINI trial			
	MADDS Aphadania Saara Carrolations	AXS-05		
	MADRS Anhedonia Score Correlations	Within-subject Correlation Coefficient (95% CI)	P value	
,	SDS Total Score	0.75 (0.72, 0.78)	<.001	
	Work/School	0.64 (0.59, 0.68)	<.001	
	Social Life	0.72 (0.68, 0.75)	<.001	
	Family Life/Home Responsibilities	0.68 (0.65, 0.72)	<.001	

MADRS, Montgomery-Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale.

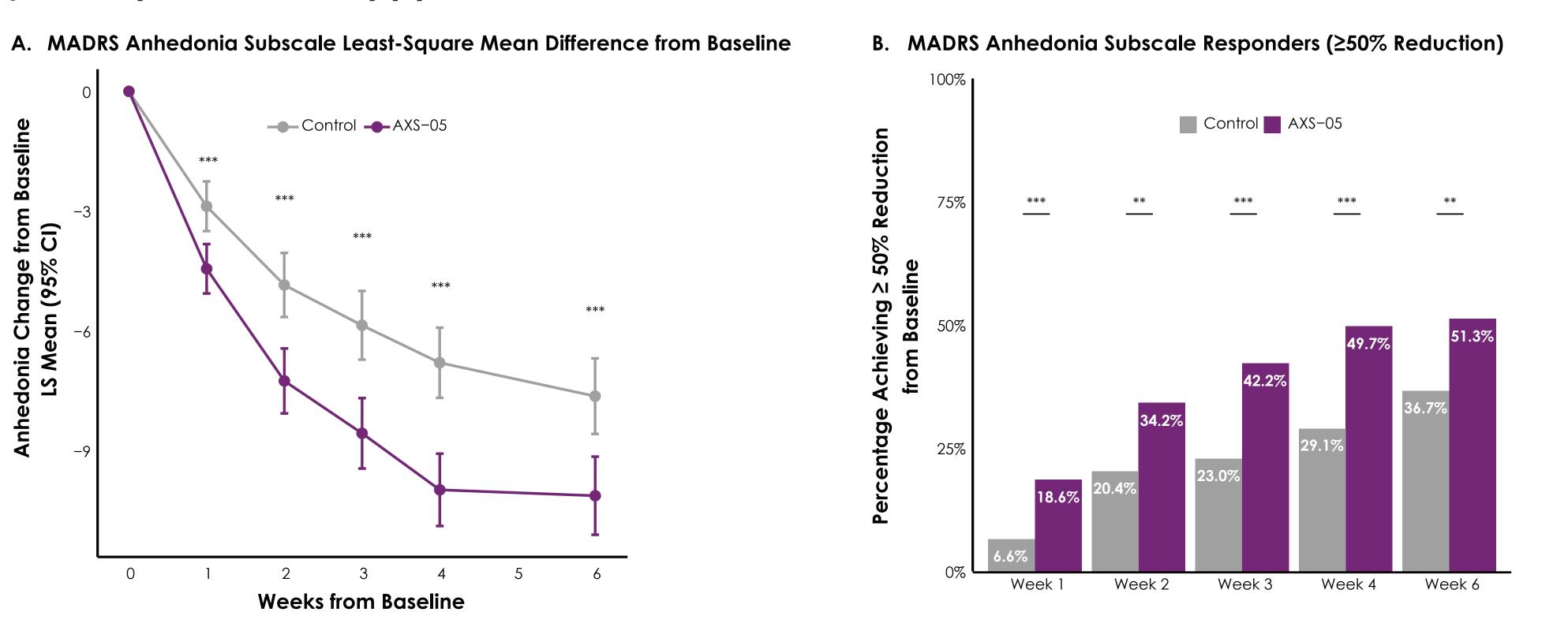
There were positive correlations (0.75 correlation coefficient; P<.001) between MADRS Anhedonia subscale and SDS scores over the 6-week treatment period with AXS-05 (Table 2)

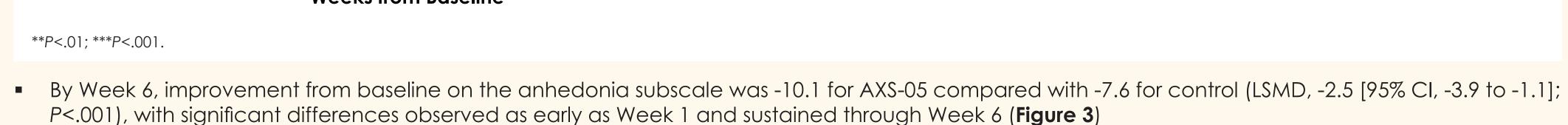
■ The most commonly reported adverse reactions (≥5% and twice the rate of placebo) with AXS-05 were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis

Anhedonia subscale

*P<.05;**P<.01; ***P<.001.

Figure 3. MADRS Anhedonia Subscale Least-Square Mean Difference from Baseline (A) and Responders (≥50% Reduction) (B)





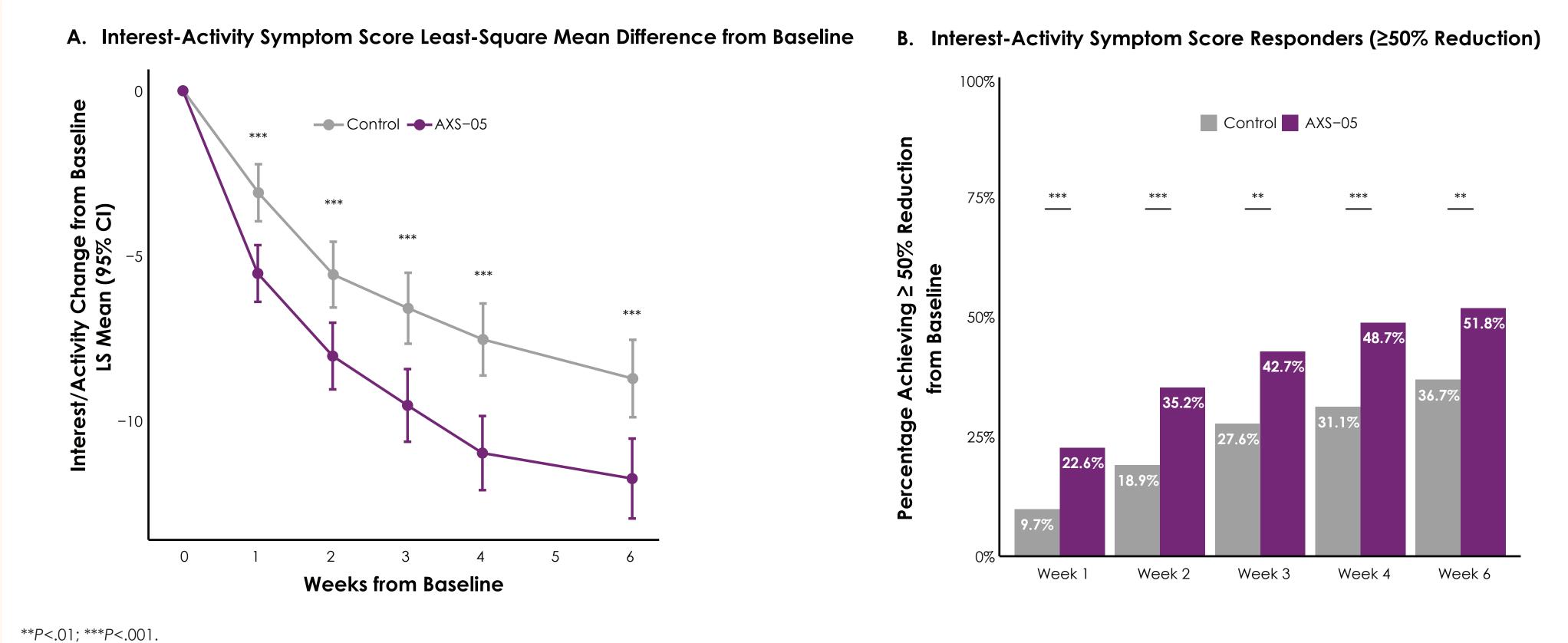
• Rates of response in anhedonia symptoms were significantly greater for AXS-05 (18.6%) vs control (6.6%) at Week 1 (P<.001) and at every timepoint

Weeks from Baseline

Interest-activity symptom score

and sustained through Week 6 (Figure 4)





12. Thoughts of death/suicide

3. General interest

14. Energy level

15. Feeling slowed down

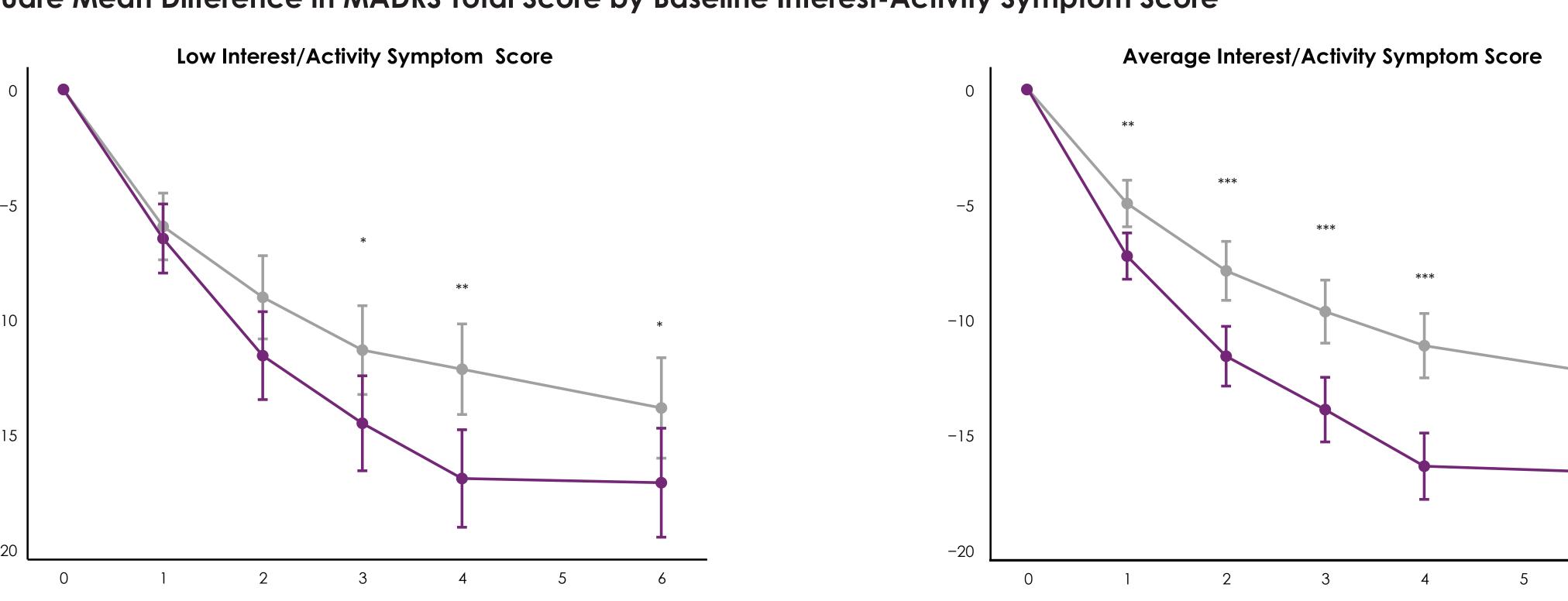
16. Feeling restless

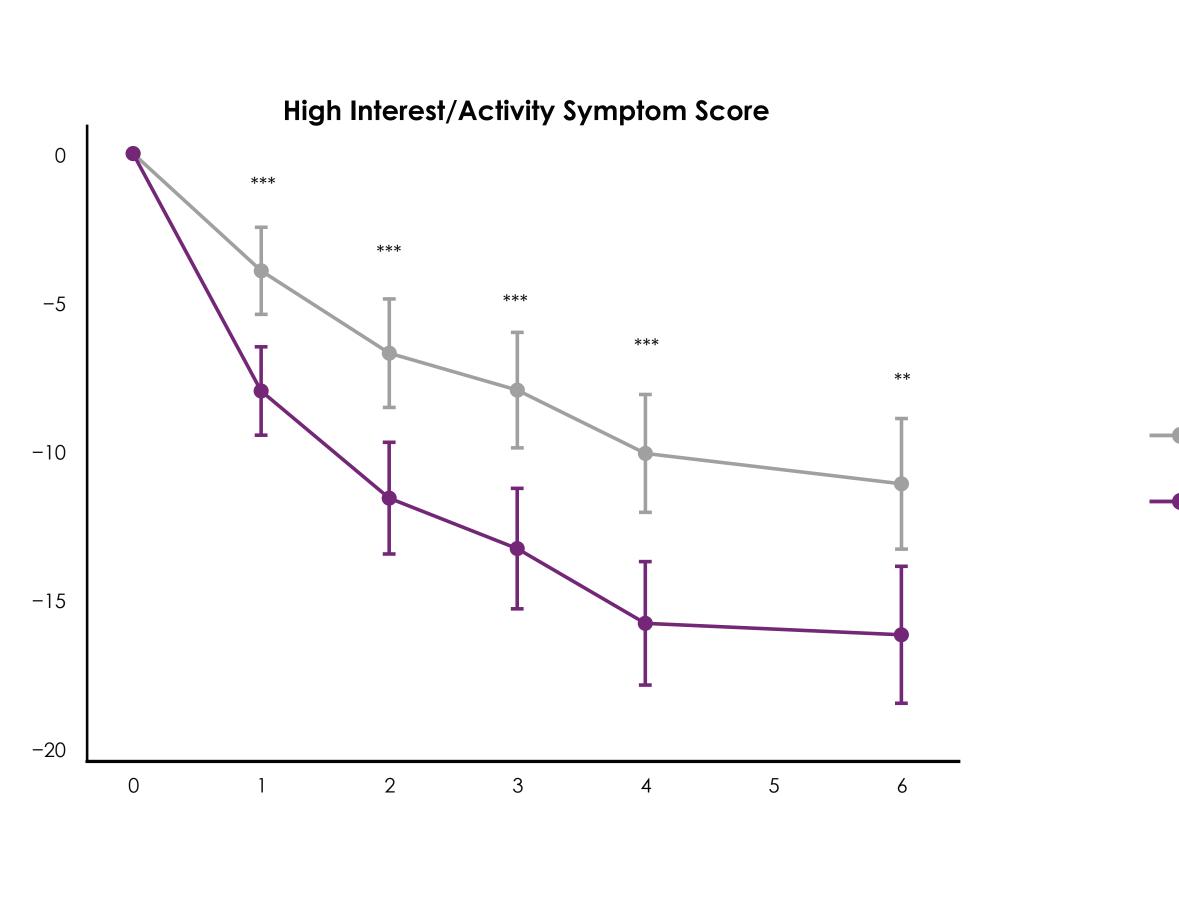
■ By Week 6, the LSMD from baseline for AXS-05 vs control was -3.0 (95% CI, -4.7 to -1.3; P<.001); significant differences were observed as early as Week 1

 Rates of response based on Interest-Activity symptom score were significantly greater for AXS-05 (22.6%) compared with control (9.7%) at Week 1 (P<.001) and remained significantly greater at every timepoint thereafter

Difference from control on MADRS total score at low, average, and high baseline activity symptom score

Figure 5. Least-Square Mean Difference in MADRS Total Score by Baseline Interest-Activity Symptom Score





• At week 1, AXS-05 significantly improved MADRS total score from baseline in patients with average interest-activity score (ie, more severe; P<.001) and maintained through Week 6 (Figure 5)

• Significant improvements for participants with low Interest-Activity score treated with AXS-05 were observed starting at Week 3 (P=.025) and were maintained through Week 6