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

Roger S McIntyre,[1-3] Sagar V Parikh,[4] Rakesh Jain,[5] Zachariah Thomas,[6] Graham Eglit,[7] Andrew J Cutler[8]

[1]University of Toronto, Toronto, ON, Canada; [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [3]Department of Pharmacology, University of Toronto, Toronto, ON, Canada; [4]University of Michigan, Ann Arbor, MI, USA; [5]Department of Psychiatry, Texas Tech University School of Medicine-Permian Basin, Midland, TX, USA; [6]Formerly of Axsome Therapeutics, Inc., New York, NY, USA; [7]Axsome Therapeutics Inc., New York, NY, USA; [8]Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA

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

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 MDD[3]; it is also associated with functional impairment, reduced 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 patient outcomes[7]
- 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 dysfunction in the pathogenesis of depression[8,9]
  - Clinical evidence suggests that glutamatergic modulation can be effective at improving measures of anhedonia in patients with MDD[10]
- There is an urgent clinical need for new treatment modalities that can effectively resolve the broad range of depression symptoms, particularly anhedonia, and improve functional impairment associated with MDD

Figure 1. AXS-05 Mechanism of Action

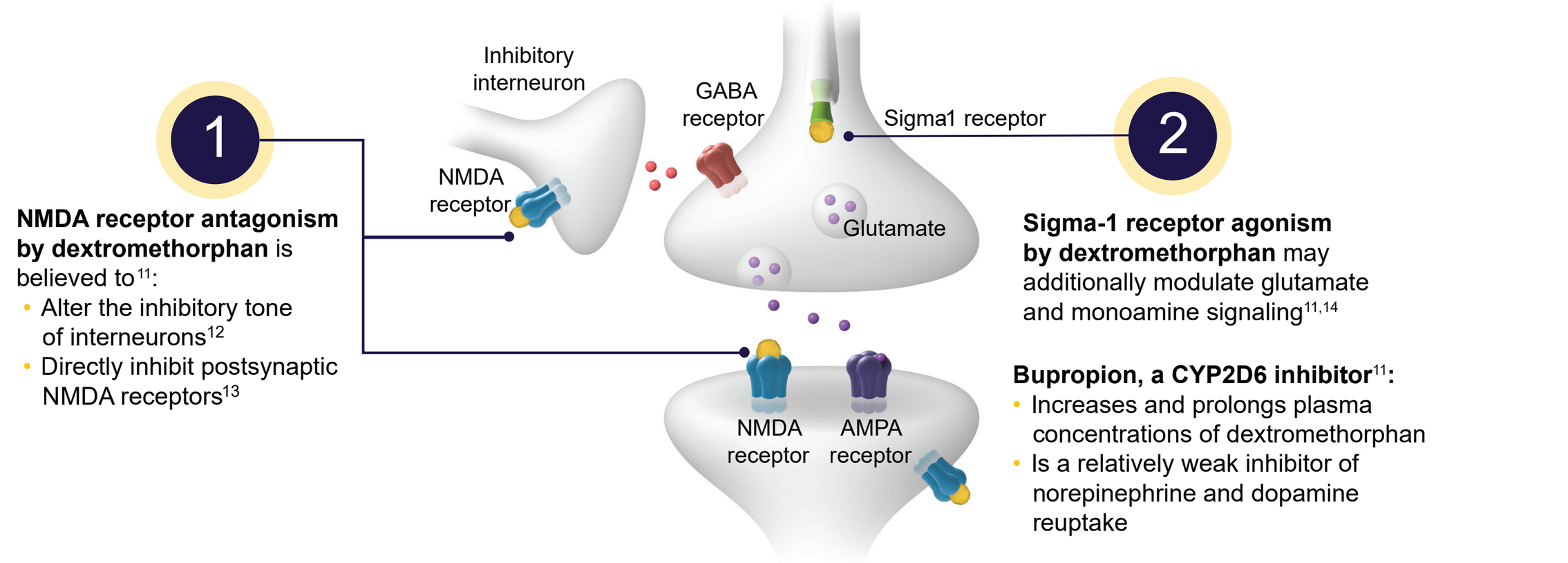

1
NMDA receptor antagonism by dextromethorphan is believed to[11]:
• Alter the inhibitory tone of interneurons[12]
• Directly inhibit postsynaptic NMDA receptors[13]
Inhibitory interneuron
NMDA receptor
GABA receptor
Sigma1 receptor
Glutamate
NMDA receptor
AMPA receptor
2
Sigma-1 receptor agonism by dextromethorphan may additionally modulate glutamate and monoamine signaling[11,14]
Bupropion, a CYP2D6 inhibitor[11]:
• Increases and prolongs plasma concentrations of dextromethorphan
• Is a relatively weak inhibitor of norepinephrine and dopamine reuptake

Figure adapted from reference 15: Kadriu B, et al. *Int J Neuropsychopharmacol.* 2019;22(2):119-35.
AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA; gamma-aminobutyric acid; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate.

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]
  - 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 agonism is also associated with anti-inflammatory and neuroprotective activity
  - The bupropion component of AXS-05 is an aminoketone and a CYP2D6 inhibitor that serves to increase the bioavailability of dextromethorphan by inhibiting its metabolism, and it is a weak norepinephrine and dopamine reuptake inhibitor[13,16]

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 (control)

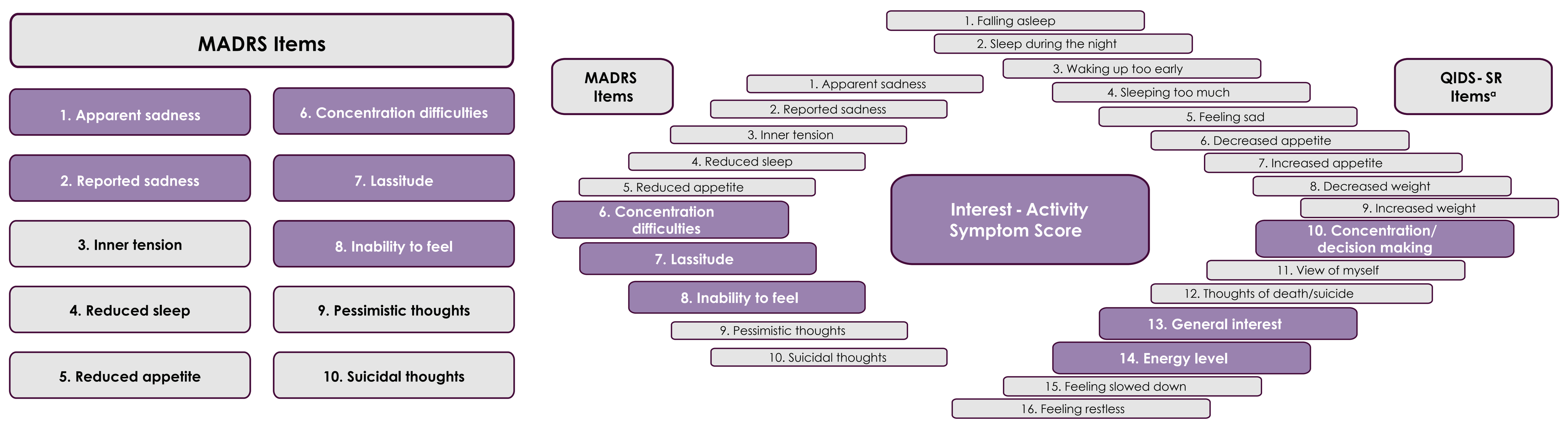
Post hoc analyses

- 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 interest-activity 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 Scale; GEMINI only)

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


A. MADRS Anhedonia Sub Score
MADRS Items
1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts
B. Interest-Activity Symptom Score from MADRS and QIDS-SR
MADRS Items
Interest - Activity Symptom Score
QIDS- SR Items[a]
1. Falling asleep
2. Sleep during the night
3. Waking up too early
4. Sleeping too much
5. Feeling sad
6. Decreased appetite
7. Increased appetite
8. Decreased weight
9. Increased weight
10. Concentration/ decision making
11. View of myself
12. Thoughts of death/suicide
13. General interest
14. Energy level
15. Feeling slowed down
16. Feeling restless

[a]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.

RESULTS

Study population

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

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)

[a]ASCEND, bupropion; GEMINI, placebo. [b]n=198. [c]Maximum MADRS anhedonia score is 30. [d]Maximum Interest-Activity score is 36. [e]GEMINI 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

MADRS Anhedonia Score Correlations	AXS-05	
	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.

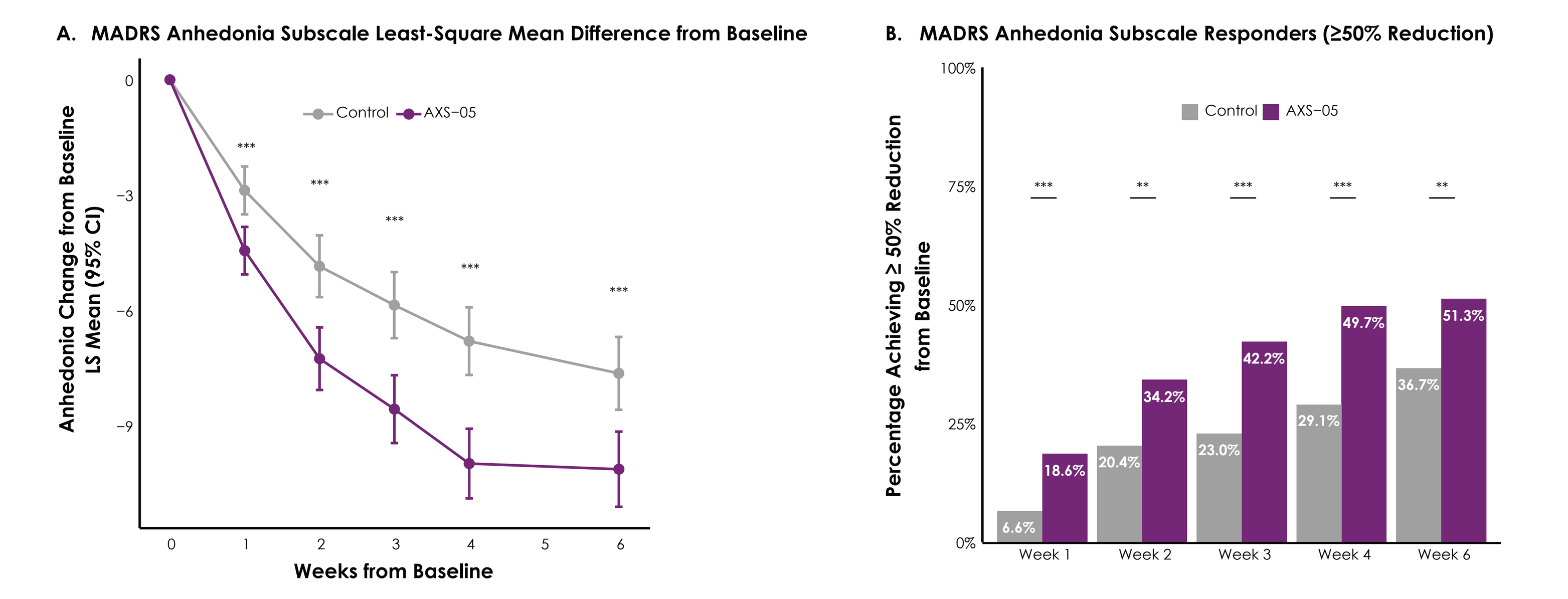
- There were positive correlations (0.75 correlation coefficient; P<.001) between MADRS Anhedonia subscale and SDS scores over the 6-week treatment period with AXS-05 (**Table 2**)

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

Anhedonia subscale

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

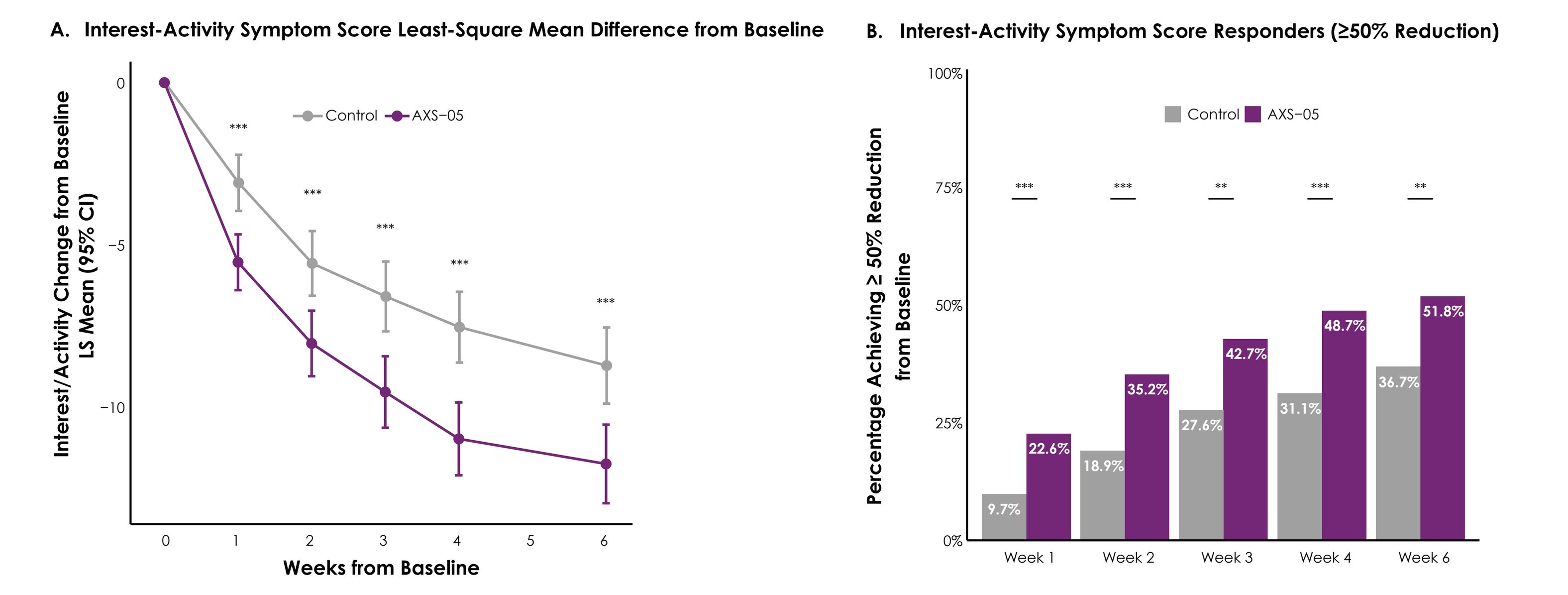

A. MADRS Anhedonia Subscale Least-Square Mean Difference from Baseline
Control
AXS-05
Anhedonia Change from Baseline LS Mean (95% CI)
Weeks from Baseline
B. MADRS Anhedonia Subscale Responders (≥50% Reduction)
Percentage Achieving ≥ 50% Reduction from Baseline
6.6%
18.6%
20.4%
34.2%
23.0%
42.2%
29.1%
49.7%
36.7%
51.3%
Week 1
Week 2
Week 3
Week 4
Week 6

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

- By Week 6, improvement from baseline on the anhedonia subscale was -10.1 for AXS-05 compared with -7.6 for control (LSMD, -2.5 [95% CI, -3.9 to -1.1]; P<.001), with significant differences observed as early as Week 1 and sustained through Week 6 (**Figure 3**)
- 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 thereafter

Interest-activity symptom score

Figure 4. Interest-Activity Symptom Score Least-Square Mean Difference from Baseline (A) and Responders (≥50% Reduction) (B)

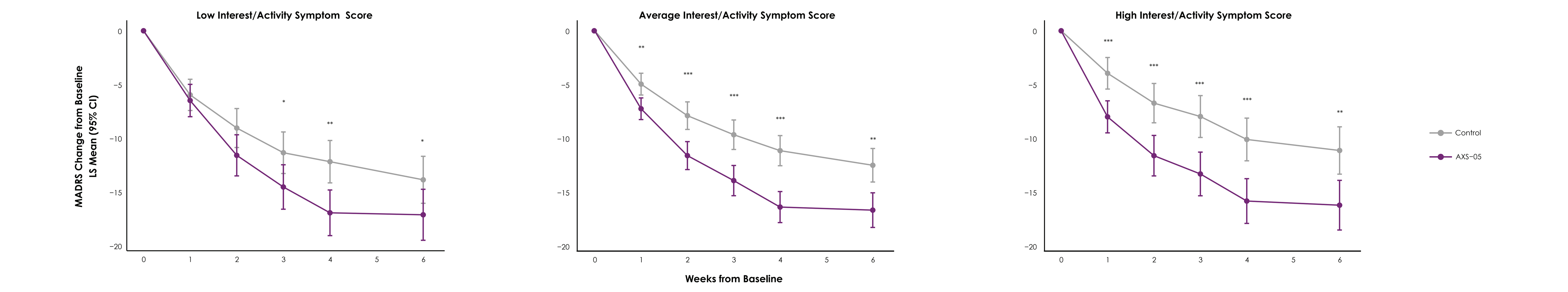

A. Interest-Activity Symptom Score Least-Square Mean Difference from Baseline
Control
AXS-05
Interest/Activity Change from Baseline LS Mean (95% CI)
Weeks from Baseline
B. Interest-Activity Symptom Score Responders (≥50% Reduction)
Percentage Achieving ≥ 50% Reduction from Baseline
9.7%
22.6%
18.9%
35.2%
27.6%
42.7%
31.1%
48.7%
36.7%
51.8%
Week 1
Week 2
Week 3
Week 4
Week 6

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

- 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 and sustained through Week 6 (**Figure 4**)
- 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



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

- At week 1, AXS-05 significantly improved MADRS total score from baseline in patients with average interest-activity score (P=.002), and high 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

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G Eglit is a employee of Axsome Therapeutics Inc. **Z Thomas** was an employee of Axsome Therapeutics and may hold stock in the company.

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