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 outcomes⁷
- N-methyl-D-aspartate (NMDA) receptor antagonism has been shown to have antidepressant effects in animal models and clinical trials, establishing the role of glutamatergia dysfunction in the pathogenesis of depression^{8,7} - 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 modalities that can effectively resolve the broad rang of depression symptoms, particularly anhedonia, and improve functional impairment associated with MDD

RESULTS

Study population

Table 1. Baseline Demographics and Clinical Characteristics (ASCEND/GEMINI)			
Parameter	AXS-05 (n=199)	Controlª (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)	
	/INI and ASCEND were similar between AXS-05 and control arms (1	Table 1)	
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	

(Table 2)

Safety

dysfunction, and hyperhidrosis



Study design



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 pioavailability of dextromethorphan by inhibiting its metabolism, and it is a weak norepinephrine and dopamine reuptake inhibitor^{13,16}

- n=156; placebo, n=162)¹⁷

(control)

Post hoc analyses

13, 14) (Figure 2)

Key analyses

- activity score
- Interest-Activity symptom score
- Scale; GEMINI only)

aseline Demographics and	Clinical Characteristics (ASCEND/GEMINI)

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

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

Week 2 Week 3 Week 4 Week 6 Weeks from Baseline **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

• 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

- 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

• 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,

Least square mean difference (LSMD) from baseline in the MADRS anhedonia sub score and interest-

■ Percentage of responders (participants achieving ≥50% reduction) in MADRS anhedonia sub score and

 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)



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



. MADRS Anhedonia Subscale Responders (\geq 50% Reduction)



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

Interest-activity symptom score

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

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





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

^{*}P<.05;**P<.01; ***P<.001.