Anxiolytic Effects of Auvelity® (Dextromethorphan-Bupropion): Post Hoc Analyses Across Trials in Major Depressive Disorder

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Key Objective

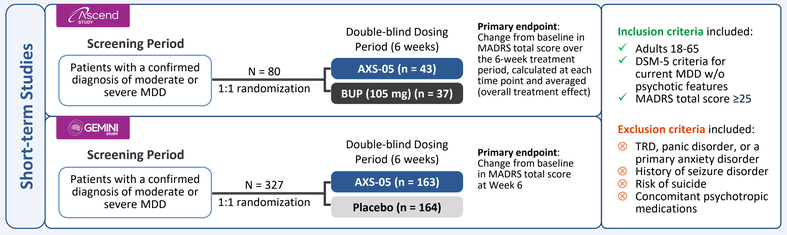
Evaluate the anxiolytic efficacy and anxiety-related safety of dextromethorphan-bupropion in patients with major depressive disorder through post hoc analyses of four clinical trials

Introduction

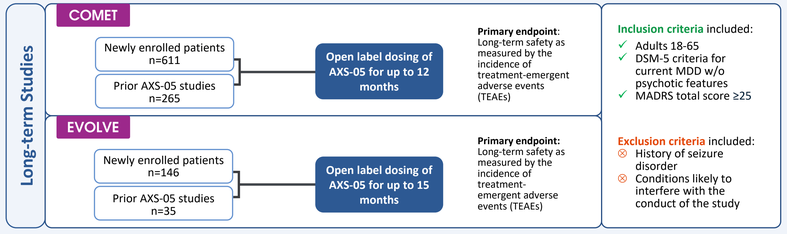
- Anxiety is common in major depressive disorder (MDD), with anxious distress reported in 45-78% of patients[1-5]
- Anxiety – whether a symptom of MDD or a comorbid disorder – is linked to poorer outcomes, including reduced quality of life, impaired social functioning, and increased suicidality[6-8]
- Because anxiety symptoms influence clinicians' antidepressant selection,[9] evaluating treatment effects on both depressive and anxious symptoms is essential
- Here, we examine the anxiolytic efficacy and safety of dextromethorphan-bupropion (45 mg/105 mg) (AXS-05; DM-BUP; Auvelity®), an N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and CYP2D6 inhibitor approved for the treatment of MDD in adults[10,11]

Methods

- The **ASCEND** Phase 2 and **GEMINI** Phase 3 studies assessed efficacy, tolerability, and safety of AXS-05 vs active control bupropion (BUP 105 mg) or placebo, respectively, in participants with moderate to severe MDD[5,6]
- Patients with anxiety were not excluded if anxiety had not been the primary focus of clinical attention during the 6 months prior to screening



- The **COMET** study was a long-term, Phase 3, open label, multi-center, safety and efficacy study (N=876)
- The **EVOLVE** study was an open-label trial: MDD patients with at least one prior treatment failure were treated with AXS-05 (N=181)
- Patients with anxiety were not excluded



BID, twice-daily; BUP, bupropion; DM, dextromethorphan; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; TRD, treatment resistant depression.

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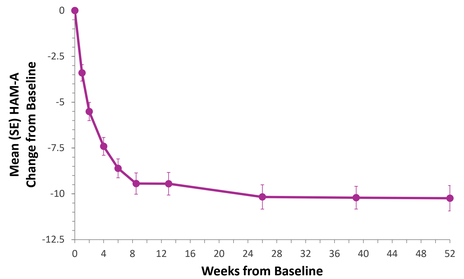
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Results

HAM-A (EVOLVE)

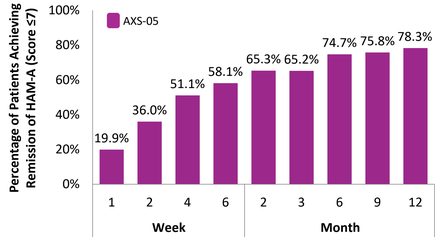
Figure 1: Change from Baseline in HAM-A Total Score Over Time in the EVOLVE Trial[a]



	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Mo 2	Mo 3	Mo 6	Mo 9	Mo 12
n[a] =	145	141	136	131	124	118	112	95	91	83
HAM-A Score[b]	15.6	12.3	10.0	8.0	6.8	6.1	5.9	5.2	5.0	4.6
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

- Treatment with AXS-05 statistically significantly improved (reduced) HAM-A total score from a baseline mean of 15.63 by 3.40±0.45 (mean±SE) at Week 1, 5.51±0.50 at Week 2, 8.61±0.52 at Week 6, and 10.24±0.69 at Month 12 (*P*<0.001 for all) (**Fig. 1**)

Figure 2: HAM-A Remission (Score ≤ 7) in the EVOLVE Trial



- By Week 4, over 50% of participants had achieved remission of anxiety symptoms (HAM-A≤7), with 78.3% of participants remitting at Month 12

[a]mITT direct entry, newly enrolled participants.
[b]Mean.
HAM-A, Hamilton Anxiety Rating Scale; Mo, month; mITT, Modified Intention to Treat; SE, standard error; Wk, week.

HAM-A : MADRS Item Correlation

Table 1: Correlation Between HAM-A Total Score & MADRS Inner Tension Item in the EVOLVE Trial[a]

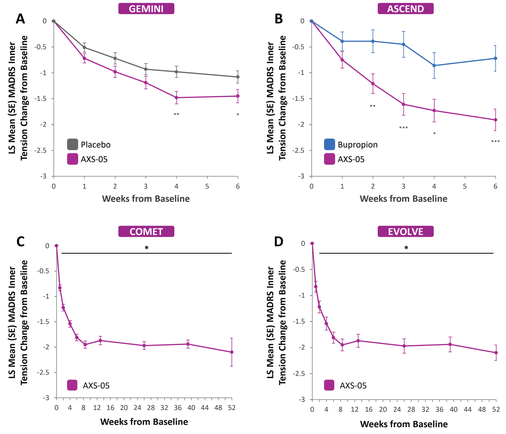
Group	Correlation Coefficient[b] (95% CI)	*P*-Value
Week 1	0.57 (0.44, 0.67)	<0.001
Week 6	0.60 (0.47, 0.70)	<0.001
Month 12	0.62 (0.46, 0.74)	<0.001

- Higher HAM-A total scores were associated with higher MADRS Inner Tension item scores throughout treatment

[a]mITT Population.
[b]Correlation coefficient reflects Spearman's rank correlation.
CI, confidence interval; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, Modified Intention to Treat.

MADRS Inner Tension Item

Figure 3: Change from Baseline in MADRS Inner Tension Item Over Time Across Trials



- AXS-05 significantly reduced Inner Tension scores over time compared to placebo (GEMINI: Δ=0.37 at Week 6, *P*=0.034) and bupropion (ASCEND: Δ=1.19 at Week 6, *P*<0.001) (**Fig. 3A, B**)
- In the open-label extension studies (**Fig. 3C, D**), AXS-05-treated participants had statistically significant reductions from baseline in Inner Tension scores of 0.86 and 0.83 (EVOLVE and COMET), 1.98 and 1.81, and 2.48 and 2.10 at Week 1, Week 6, and Month 12, respectively (*P*<0.001 for all)

*P < 0.05, **P < 0.01, ***P < 0.001.
CI, confidence interval; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SE, standard error.

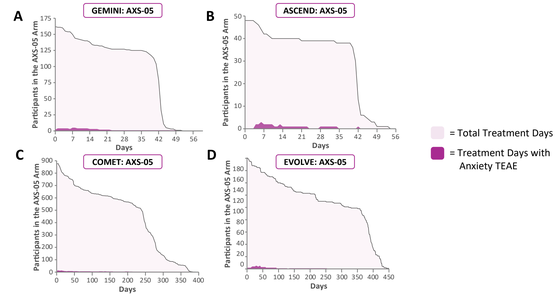
Safety

Table 2: Overall Summary of Anxiety Treatment–Emergent Adverse Events[a]

Treatment Groups	No. of Events	n (%)	Median Duration (Min, Max)	Absolute Prevalence[b]	AE Leading to Study Discontinuation (%)
GEMINI					
AXS-05	7	7 (4.3%)	13 (2, 31)	1.8%	3 (1.9%)
Placebo	2	2 (1.2%)	20 (1, 39)	0.6%	0 (0%)
ASCEND					
AXS-05	6	5 (10.4%)	4 (1, 20)	2.1%	2 (4.2%)
Bupropion	1	1 (2.1%)	2 (2, 2)	0.1%	0 (0%)
COMET					
AXS-05	36	34 (3.9%)	10 (1, 312)	0.9%	7 (0.8%)
EVOLVE					
AXS-05	7	7 (3.9%)	44 (5, 120)	0.9%	0 (0%)

- Anxiety TEAEs were relatively uncommon across the four studies
- Events were generally short in duration (median 4-44 days) and led to discontinuation in a small proportion of AXS-05-treated participants (0-4.2% cases across trials)

Figure 4: Absolute Prevalence of Anxiety TEAEs



- Absolute prevalence (the ratio of participant days with a TEAE to the total number of participant treatment days) of anxiety TEAEs ranged from 0.9-2.1% for AXS-05-treated participants

[a]Safety Population (includes all subjects who receive at least 1 dose of AXS-05).
[b]Absolute prevalence was defined as the ratio of participant days with anxiety TEAEs to the total number of participant treatment days.
AE, adverse event; Max, maximum; Min, minimum; No., number; TEAE, treatment emergent adverse events.

Conclusions

- AXS-05 was associated with meaningful improvement in anxiety symptoms in adults with MDD
- In a long-term, open-label study, HAM-A total scores significantly improved, with more than 75% of participants achieving anxiety remission by Month 12
- Across both open-label and randomized studies, improvements were observed in the MADRS Inner Tension item, with separation from control groups observed in the randomized studies
- Anxiety TEAEs were infrequent, generally transient, and led to few study discontinuation
- Taken together, these findings highlight the potential anxiolytic efficacy and safety of AXS-05 in patients with MDD