Effects of Auvelity® (Dextromethorphan-Bupropion) in Participants with Major Depressive Disorder and Anxious Distress

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Objective

Evaluate the antidepressant efficacy of dextromethorphan-bupropion in participants with major depressive disorder and anxious distress.

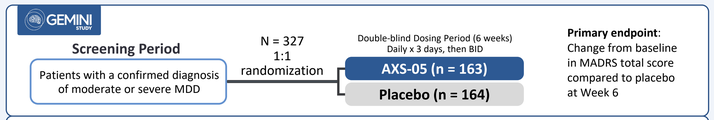
Introduction

- Anxiety is a highly prevalent feature of major depressive disorder (MDD), with anxious distress reported in 45-78% of people with MDD[1-5]
- The DSM-5-TR 'with anxious distress' specifier requires ≥2 of 5 symptoms during a depressive episode[6]:
  - Feeling keyed up or tense
  - Feeling unusually restless
  - Difficulty concentrating due to worry
  - Fear that something awful may happen
  - Feeling that one might lose control
- The presence of anxiety symptoms in MDD is associated with a decreased likelihood of response to antidepressant treatment (ADT)[2,5]
- Dextromethorphan-bupropion (45mg/105mg) (AXS-05; Auvelity®) is an NMDA receptor antagonist, sigma-1 receptor agonist, and CYP2D6 inhibitor approved for the treatment of MDD in adults[7-9]
- Given the impact of anxious distress on response to ADTs, this post-hoc analysis was conducted to examine the antidepressant efficacy of dextromethorphan-bupropion in participants with MDD and anxious distress

ADT, antidepressant treatment; BUP, bupropion; CYP2D6, cytochrome P450 2D6; DM, dextromethorphan; DM-BUP, dextromethorphan-bupropion; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition – Text Revision; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate.

Methods

- **GEMINI** Phase 3 study assessed efficacy, tolerability, and safety of AXS-05 vs placebo in participants with moderate to severe MDD[5,10]
- Patients with anxiety were not excluded if anxiety had not been the primary focus of clinical attention during the 6 months prior to screening



Inclusion criteria included:
- ✓ Adults 18-65
- ✓ DSM-5 criteria for current MDD w/o psychotic features
- ✓ MADRS total score of ≥25

Exclusion criteria included:
- ⊗ TRD, panic disorder, or a primary anxiety disorder
- ⊗ History of seizure disorder
- ⊗ Risk of suicide
- ⊗ Concomitant psychotropic medications

- Participants were categorized post hoc as *with* anxious distress or *without* anxious distress using a proxy definition aligned with the DSM-5-TR 'with anxious distress' specifier
- Continuous outcomes were analyzed using mixed models for repeated measures and categorical outcomes via chi-square tests; *P*-values are nominal

With Anxious Distress was defined as meeting **two or more** of the following three thresholds:

Concentration Difficulties
MADRS Concentration Difficulties score **≥3**
AND
QIDS Concentration Difficulties score **≥2**

Inner Tension
MADRS Inner Tension score **≥3**

Restlessness
QIDS Restlessness score **≥2**

AXS-05, dextromethorphan-bupropion; BID, twice daily; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition – Text Revision; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; QIDS, Quick Inventory of Depressive Symptomatology; TRD, treatment resistant depression.

Results

GEMINI: Participants with Anxious Distress

Figure 1: Participants in GEMINI meeting proxy criteria for Anxious Distress[a]

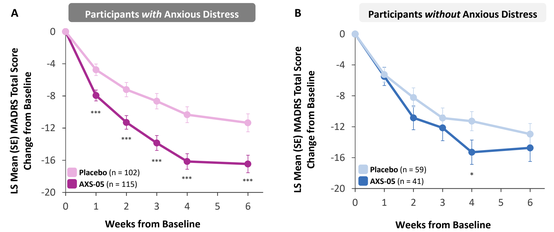


- Over two thirds of participants in GEMINI met proxy criteria for MDD with anxious distress

[a]Modified intention-to-treat population; all randomized participants who took at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment. One placebo-treated participant with missing QIDS baseline data was excluded from the anxious distress analyses.
AXS-05, dextromethorphan-bupropion; MDD, major depressive disorder.

MADRS Total Score

Figure 2: MADRS Total Score Change from Baseline Over Time

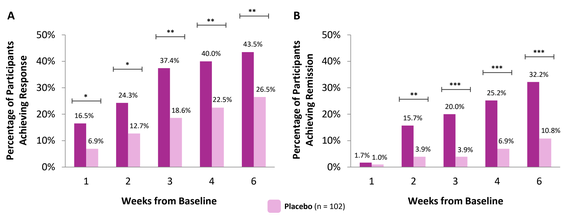


- Among participants with anxious distress, AXS-05 produced greater reductions in MADRS total score versus placebo at all timepoints (all $P \leq 0.001$)

*P < 0.05, **P < 0.01, ***P ≤ 0.001; *P*-values are nominal.
AXS-05, dextromethorphan-bupropion; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SE, standard error.

MADRS Response and Remission

Figure 3: MADRS Response and Remission Among Participants with Anxious Distress

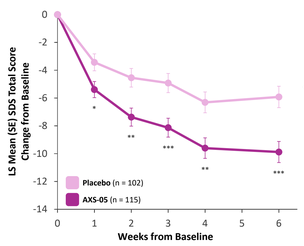


- AXS-05 treatment resulted in higher response rates at all visits (**Fig. 3A**; ≥50% reduction in MADRS total score; all $P < 0.05$) and higher remission rates from Week 2 onward (**Fig. 3B**; MADRS total score ≤10; all $P < 0.01$)

*P < 0.05, **P < 0.01, ***P < 0.001; *P*-values are nominal.
AXS-05, dextromethorphan-bupropion; MADRS, Montgomery-Åsberg Depression Rating Scale.

SDS

Figure 4: SDS Change from Baseline Among Participants with Anxious Distress

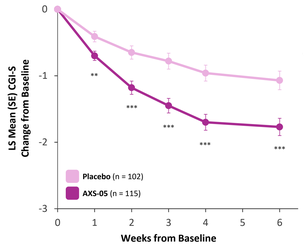


- Improvements in self-reported functional impairment, as measured by the Sheehan Disability Scale, were greater with AXS-05 versus placebo among participants with anxious distress

*P < 0.05, **P < 0.01, ***P ≤ 0.001; *P*-values are nominal.
AXS-05, dextromethorphan-bupropion; LS, least squares; SDS, Sheehan Disability Scale; SE, standard error.

CGI-S

Figure 5: CGI-S Change from Baseline Among Participants with Anxious Distress

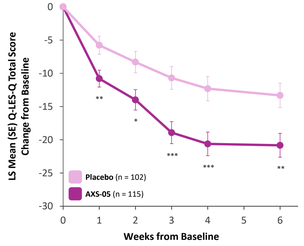


- Among participants with anxious distress, AXS-05 was associated with greater improvement in overall illness severity, as measured by the Clinical Global Impression-Severity, compared with placebo across the 6-week study period

*P < 0.05, **P < 0.01, ***P < 0.001; *P*-values are nominal.
CGI-S, Clinical Global Impressions-Severity; AXS-05, dextromethorphan-bupropion; LS, least squares; SE, standard error.

Q-LES-Q-SF

Figure 6: Q-LES-Q-SF Change from Baseline Among Participants with Anxious Distress

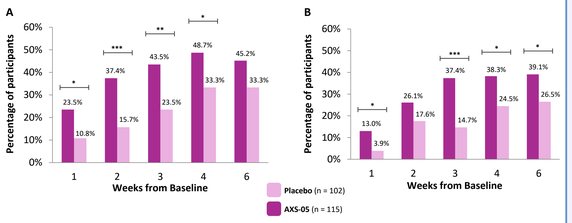


- Among participants with anxious distress, AXS-05 was associated with greater improvements in quality of life and life satisfaction, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form, compared with placebo across the 6-week treatment period

*P < 0.05, **P < 0.01, ***P ≤ 0.001; *P*-values are nominal.
AXS-05, dextromethorphan-bupropion; LS, least squares; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SE, standard error.

CGI-I and PGI-I

Figure 7: Percentage of Participants with Anxious Distress Showing Improvement on the CGI-I and PGI-I Over Time[a]



- A greater percentage of participants with anxious distress treated with AXS-05 reported *Much Improved* or *Very Much Improved* on the CGI-I (**Fig. 7A**) and PGI-I (**Fig. 7B**) compared with placebo over the majority of the study duration

*P < 0.05, **P < 0.01, ***P < 0.001; *P*-values are nominal.
[a]Participants in the top two categories of the CGI-I and PGI-I; Much Improved and Very Much Improved.
CGI-I, Clinical Global Impressions–Improvement scale; AXS-05, dextromethorphan-bupropion; LS, least squares; PGI-I, Patient Global Impressions–Improvement scale; SE, standard error.

Safety

Table 1: Safety and Tolerability

		Total		Anxious Distress	
		AXS-05 (n=162)[a]	Placebo (n=164)[a]	AXS-05 (n=119)[b]	Placebo (n=103)[b]
Any Treatment-Emergent Adverse Event		**100 (61.7%)**	**74 (45.1%)**	**71 (59.7%)**	**46 (44.7%)**
TEAEs in ≥5% of participants	Dizziness	26 (16.0%)	10 (6.1%)	20 (16.8%)	5 (4.9%)
	Nausea	21 (13.0%)	14 (8.5%)	17 (14.3%)	9 (8.7%)
	Headache	13 (8.0%)	6 (3.7%)	9 (7.6%)	4 (3.9%)
	Diarrhea	11 (6.8%)	5 (3.0%)	6 (5.0%)	4 (3.9%)
	Somnolence	11 (6.8%)	5 (3.0%)	8 (6.7%)	5 (4.9%)
	Dry mouth	9 (5.6%)	4 (2.4%)	6 (5.0%)	2 (1.9%)
	Anxiety	7 (4.3%)	2 (1.2%)	3 (2.5%)	0

- Across participants, the most commonly reported AEs were dizziness, nausea, and headache
- Rates of discontinuation due to AEs were low in both groups, 6.2% for AXS-05 and 0.6% for placebo
- Discontinuations due to anxiety were low (1.9% vs 0%)

[a]Safety population; all subjects who received study drug.
[b]Safety population • categorized as Anxious Distress.
AE, adverse event; AXS-05, dextromethorphan-bupropion; TEAEs, treatment emergent adverse events.

Conclusions

- AXS-05 demonstrated robust antidepressant efficacy in participants with MDD and anxious distress, showing improvements in MADRS severity, response, and remission compared to placebo
- Clinician-rated global impressions and patient-reported outcomes also showed improvements in participants with anxious distress
- AXS-05 was generally well-tolerated, with low rates of anxiety-related discontinuation in the GEMINI trial
- Approximately two-thirds of participants met proxy criteria for anxious distress, consistent with epidemiologic estimates in MDD
- In this post hoc analysis, dextromethorphan-bupropion was associated with improvements in depressive symptoms among participants with MDD and symptoms of anxiety

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