Meaningful Patient-Reported Outcome Improvements at Weeks 1, 2, and 6 With AXS-05 for Major Depressive Disorder: Responder Analysis of the GEMINI Trial

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Key Objective

- To evaluate the meaningfulness and impact of dextromethorphan-bupropion (DM-BUP) treatment from the perspective of patients with major depressive disorder (MDD) using patient-reported outcome (PRO) measures of symptom severity (Quick Inventory of Depressive Symptomatology [QIDS]), functioning (Sheehan Disability Scale [SDS]), and quality of life (QOL; Quality-of-Life Enjoyment and Satisfaction Questionnaire–Short Form [Q-LES-Q-SF])

Conclusions

- At Weeks 1, 2, and 6, a significantly greater proportion of patients treated with DM-BUP reported improvements considered meaningful by both patients and clinicians on patient-reported measures of MDD symptom severity (QIDS), social and occupational functioning (SDS), and QOL (Q-LES-Q-SF) compared with placebo
- These findings reinforce that treatment with DM-BUP leads to rapid (i.e., as early as 1 week) and substantial benefits for patients with MDD by improving symptom severity, functioning, and QOL that are considered meaningful by both patients and clinicians

References

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YZ, GMLE, and HT are employees of Axsome Therapeutics, Inc., and may hold shares and/or stock options in the company.

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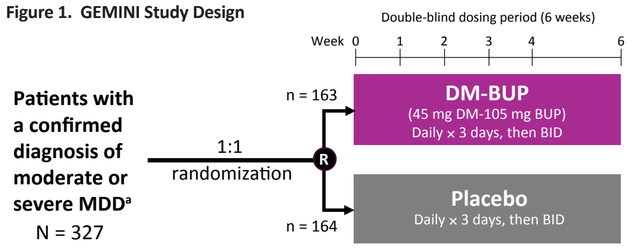
Introduction

- MDD presents with emotional, physical, and cognitive symptoms that often reduce social and occupational functioning and diminish QOL[1,2]
- Auvelity® (AXS-05, DM-BUP) is a novel, oral N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist approved for the treatment of MDD in adults[3]
- Because some MDD symptoms cannot be easily observed by clinicians and there can be discrepancies between clinician-rated outcomes and patient experiences, including QOL, PRO measures are necessary to capture patient perspectives of meaningfulness and impact of MDD treatments[4]
  - The phase 3 randomized placebo-controlled study, GEMINI (NCT04019704),[5] observed significant clinically-validated, patient- and clinician-reported outcome improvements with DM-BUP versus placebo from Week 1 through Week 6 (Figure 1); however, how meaningful these improvements were from the patient and clinician perspective has not been quantified

Figure 1. GEMINI Study Design



BID = twice daily; CGI-S = Clinician Global Impression of Severity; MADRS = Montgomery-Åsberg Depression Rating Scale.

[a] MADRS score ≥ 25 and CGI-S score ≥ 4.

Methods

- Post hoc analyses of the GEMINI study evaluated whether improvements in patient-reported symptom severity (QIDS), functioning (SDS), and QOL (Q-LES-Q-SF) at Weeks 1, 2, and 6 were considered meaningful to both patients and clinicians (Figure 2)
- Responder thresholds (i.e., the number of points of change from baseline that are considered meaningful to patients and clinicians) were established using anchor-based methods using responses from Patient Global Impression of Improvement (PGI-I) and Clinician Global Impression of Improvement (CGI-I) measures and confirmed with cumulative distribution functions[6]

Figure 2. Post Hoc PRO Analyses of GEMINI

Anchor-based methods and pooled data from both study arms were used to estimate PRO responder thresholds

Used Week 6 results for PGI-I and CGI-I to identify meaningful responder thresholds

- **PGI-I:** Estimated PRO thresholds were based on mean change from baseline among patients with "Much Improvement" and among patients with "Very Much Improvement"
- **CGI-I:** Estimated PRO thresholds were based on mean change from baseline among patients with "Moderate Improvement" and among patients with "Marked Improvement"

Thresholds were confirmed by Week 6 cumulative distribution functions

Responder proportions were calculated

Differences were tested using chi-square or Fisher exact tests

Results

- Baseline sociodemographic and clinical characteristics in the GEMINI study were similar between DM-BUP and placebo groups (Table 1)[5]
- PRO-responder thresholds associated with "Much/Moderate Improvement" or "Very Much/Marked Improvement" responses on the PGI-I/CGI-I instruments were 10- and 14- point reduction on QIDS, 12- and 17-point reduction on SDS, and 23.40- and 43.25-point change on Q-LES-Q-SF, respectively (Table 2 and Figure 3)
- Based on the thresholds for "Much/Moderate Improvement" (Figure 4) and "Very Much/Marked Improvement" (Figure 5), more patients receiving DM-BUP than placebo were QIDS, SDS, and Q-LES-Q-SF responders at Weeks 1, 2, and 6

Safety

- From GEMINI, treatment-emergent adverse events occurring in ≥ 5% of patients in the DM-BUP group were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth[5]

Table 1. Baseline Sociodemographic and Clinical Characteristics From GEMINI

Characteristic	DM-BUP (N = 156)	Placebo (N = 162)
Age, years; mean (SD), range	42.1 (12.80), 18-64	41.2 (13.77), 18-65
Sex, n (%)		
Female	95 (60.9)	117 (72.2)
Male	61 (39.1)	45 (27.8)
Race, n (%)		
White	84 (53.8)	92 (56.8)
Black or African-American	58 (37.2)	54 (33.3)
Asian	9 (5.8)	8 (4.9)
Multiple[a]	3 (1.9)	2 (1.2)
Other[a]	2 (1.3)	6 (3.7)
MADRS total score[b]; mean (SD), range	33.6 (4.43), 26.0-8.0	33.2 (4.36), 25.0-46.0
CGI-S score[b]; mean (SD), range	4.6 (0.59), 4.0-6.0	4.6 (0.57), 4.0-6.0

SD = standard deviation.

[a] Categorical terms as used in GEMINI; additional details for these groups not available.

[b] Higher MADRS scores (range, 0-60) and CGI-S scores (range, 1-7) indicate more severe disease.

Source: Iosifescu et al., 2022[5]

Table 2. Clinically Meaningful Change Thresholds

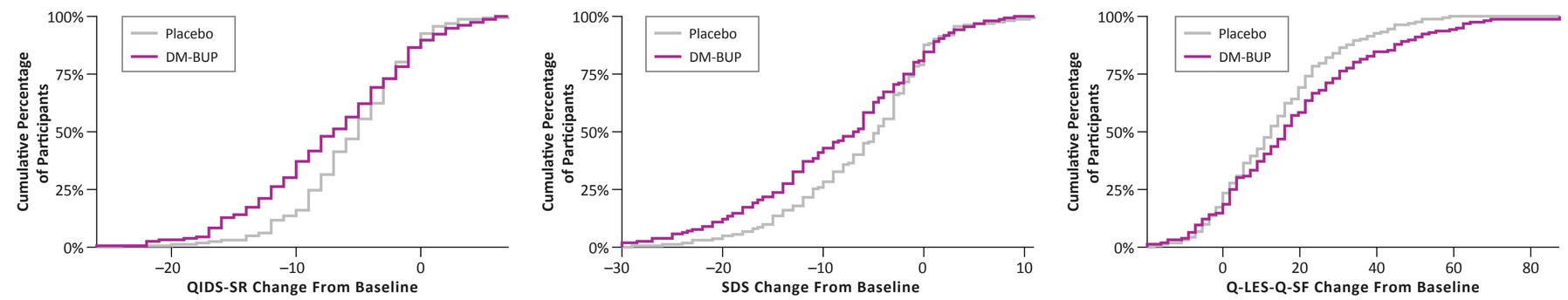
Anchor-based method	QIDS	SDS	Q-LES-Q-SF
PGI-I Much Improvement[a]	–9.36	–11. 49	23.40
CGI-I Moderate Improvement	–7.54	–9.12	20.88
Much/Moderate Improvement meaningful point change threshold[b]	**–10**	**–12**	**23.40**
PGI-I Very Much Improvement[a]	–13.13	–16.91	43.25
CGI-I Marked Improvement	–12.47	–15.54	36.63
Very Much/Marked Improvement meaningful point change threshold[b]	**–14**	**–17**	**43.25**

Note: In the modified intent-to-treat population, lower PGI-I (range, 1-7) and CGI-I (range, 1-7) scores indicate improvement.

[a] Estimated thresholds for meaningful change in QIDS, SDS, and Q-LES-Q-SF were computed as the mean change from baseline among patients achieving "Much Improvement" (PGI-I)/"Moderate Improvement" (CGI-I) or "Very Much Improvement" (PGI-I)/"Marked Improvement" (CGI-I).

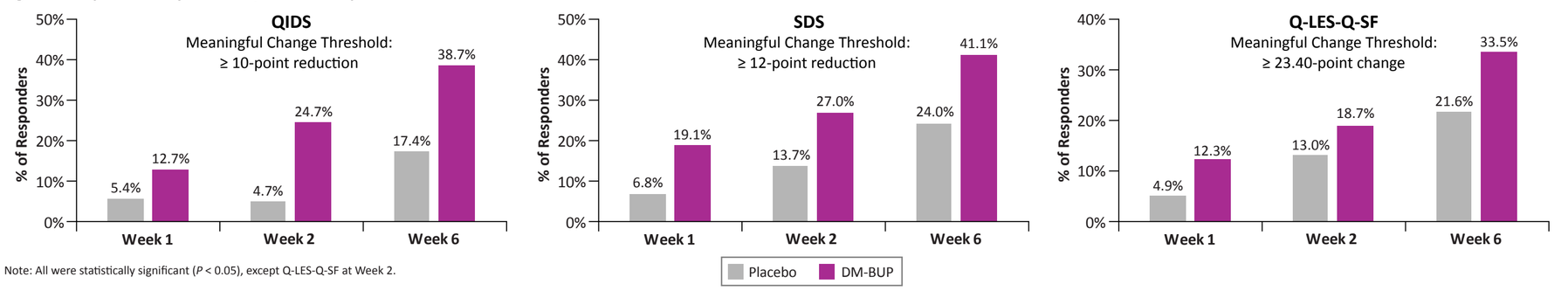
[b] Thresholds were confirmed by Week 6 cumulative distribution functions.

Figure 3. Week 6 Cumulative Distribution Function Plots



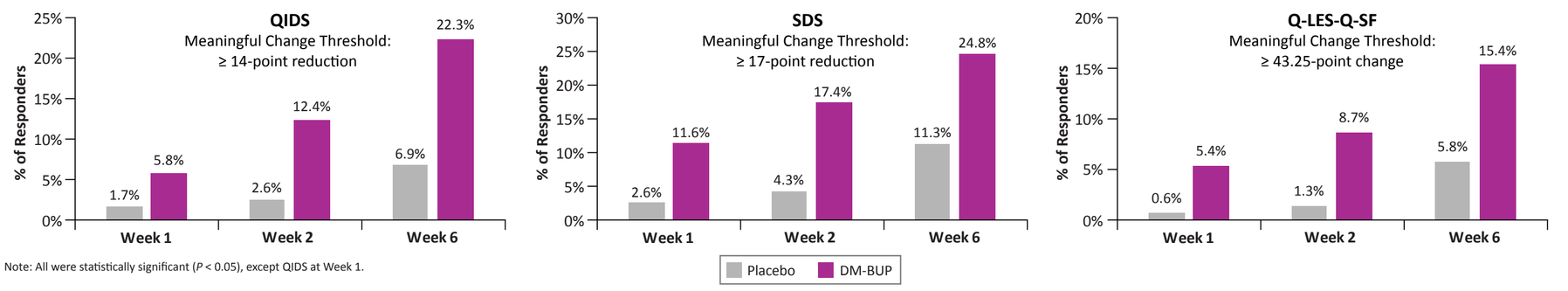
Note: Lower QIDS (range, 0-27) and SDS (range, 0-30) scores indicate improvement, whereas higher Q-LES-Q-SF (range, 14-70) total scores indicate improvement.

Figure 4. Responder Analysis: "Much/Moderate Improvement" Threshold



Note: All were statistically significant ($P < 0.05$), except Q-LES-Q-SF at Week 2.

Figure 5. Responder Analysis: "Very Much/Marked Improvement" Threshold



Note: All were statistically significant ($P < 0.05$), except QIDS at Week 1.