

# 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.

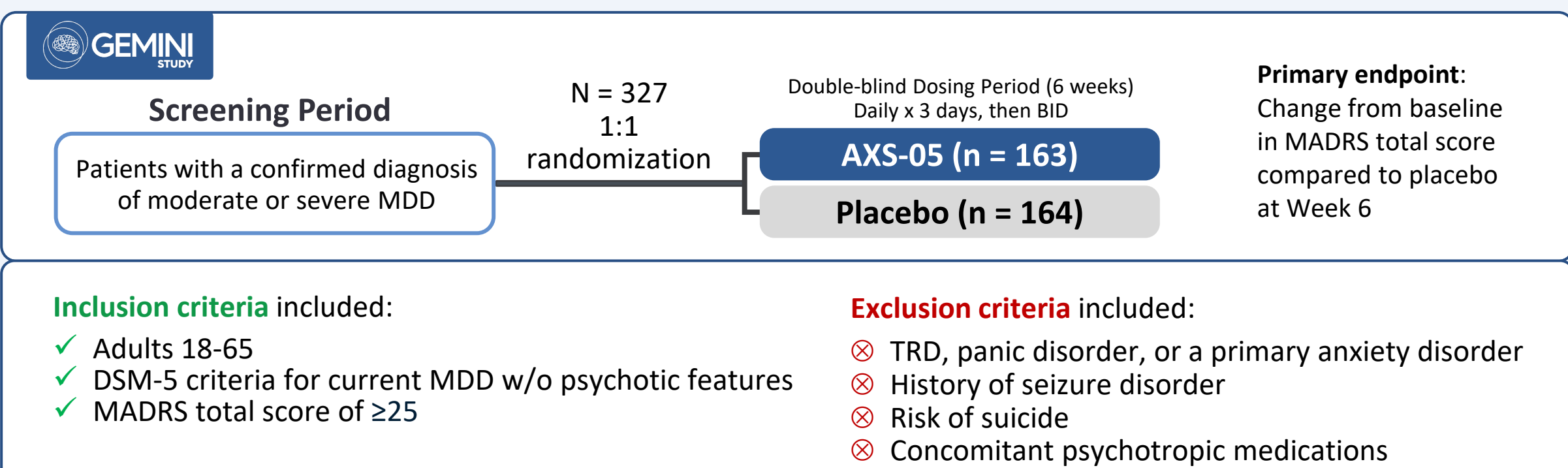
## Introduction

- Anxiety is a highly prevalent feature of major depressive disorder (MDD), with anxious distress reported in 45-78% of people with MDD<sup>1-5</sup>
- The DSM-5-TR 'with anxious distress' specifier requires  $\geq 2$  of 5 symptoms during a depressive episode<sup>6</sup>:
  - 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)<sup>2,5</sup>
- 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<sup>7-9</sup>
- 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-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<sup>5,10</sup>
- Patients with anxiety were not excluded if anxiety had not been the primary focus of clinical attention during the 6 months prior to screening



- 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:



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.

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## Disclosures

J Strawn has received research support from the National Institutes of Health and PCORI and has also received material support from Myriad Genetics. He receives royalties from Springer Publishing and Cambridge University Press, honoraria from the Neuroscience Education Institute, and serves as an author for UpToDate. Dr. Strawn has consulted for MindMed, Abbvie (Cerevel), Alkermes, Collegium, Otsuka, Sensorium, Vistagen, and Genomind. He also serves on the Speakers Bureau for Abbvie, Collegium and Myriad. R McIntyre has received research grant support from CIRM/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Johnson & Johnson, Alkermes, Neurona Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Sage, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, MindMed, Neurocrine, Neurawell, Supernus, Bauch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatrix, Abbvie, and Atai Life Sciences. S Alter, C Zeni, C Streicher, and GM Egli are employees of Axsome Therapeutics, Inc.

## Acknowledgments

These studies were funded by Axsome Therapeutics, Inc. Under the direction of the authors, Stephanie Marcus, PhD, MPA, of Axsome Therapeutics, Inc., provided medical writing and editorial support for this poster.

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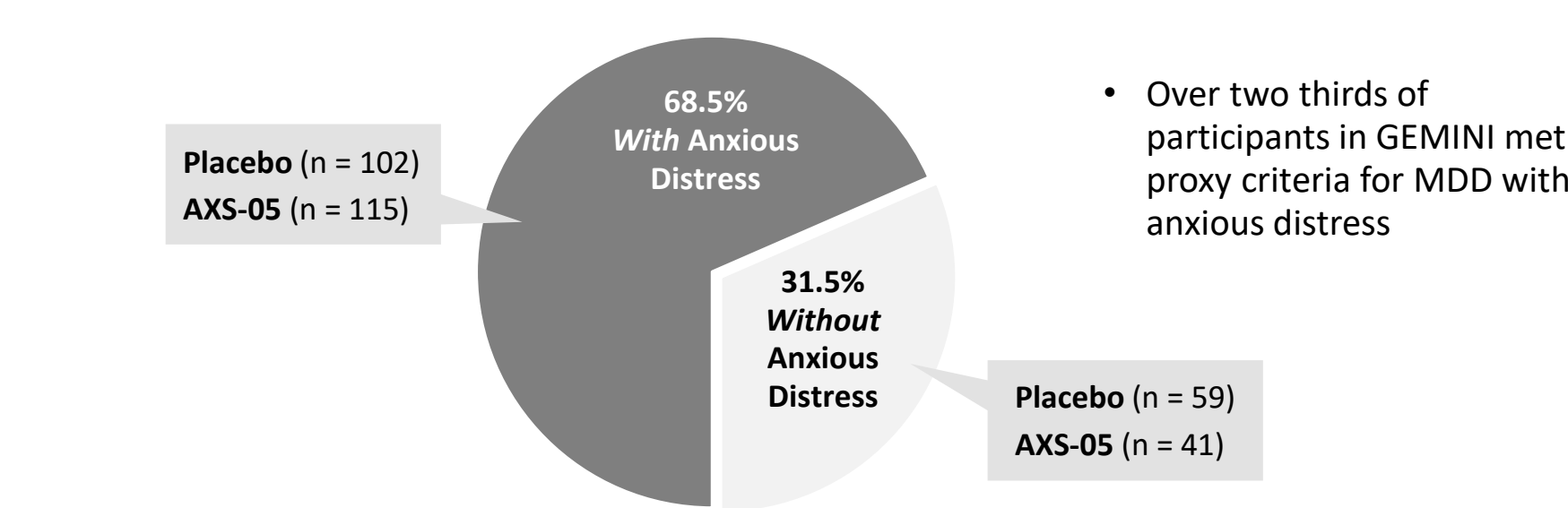
**National Network of Depression Centers Annual Conference; October 19-20, 2026; Austin, Texas**



## Results

### GEMINI: Participants with Anxious Distress

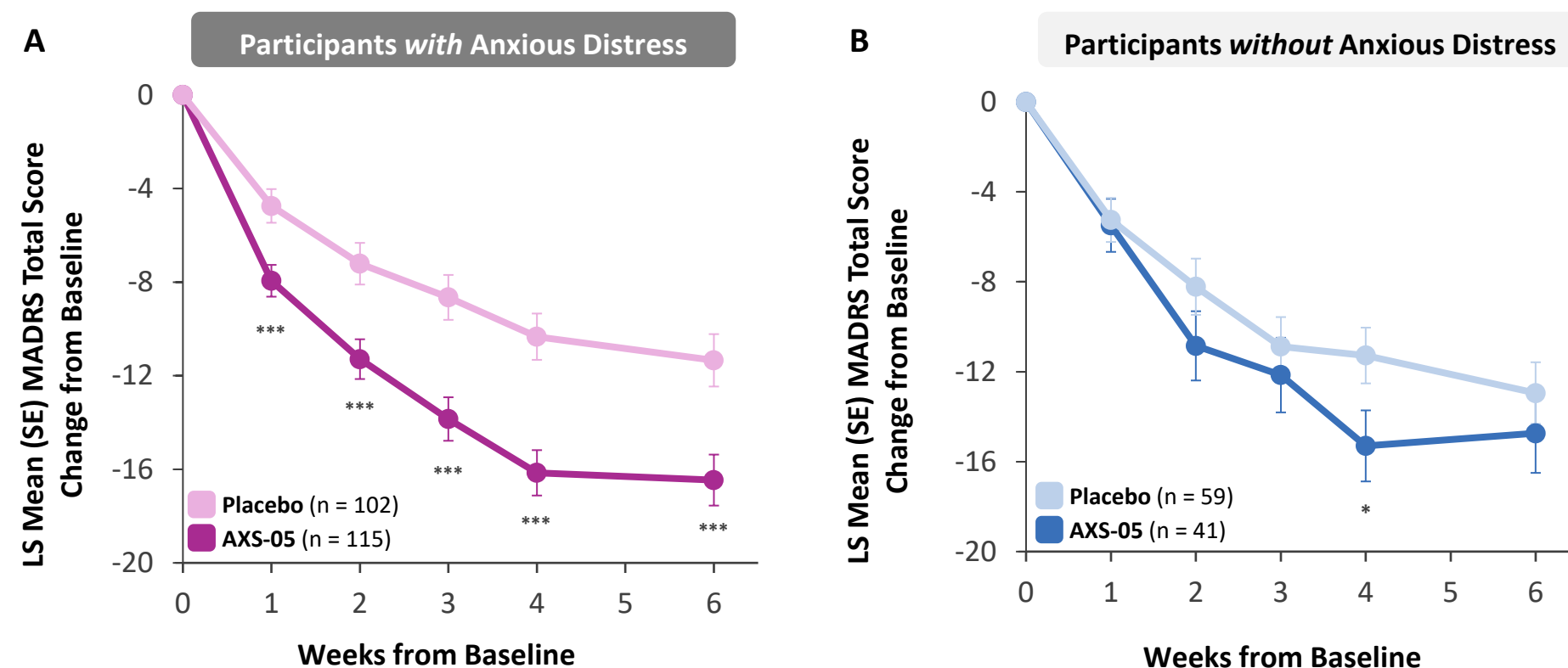
Figure 1: Participants in GEMINI meeting proxy criteria for Anxious Distress<sup>a</sup>



<sup>a</sup>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

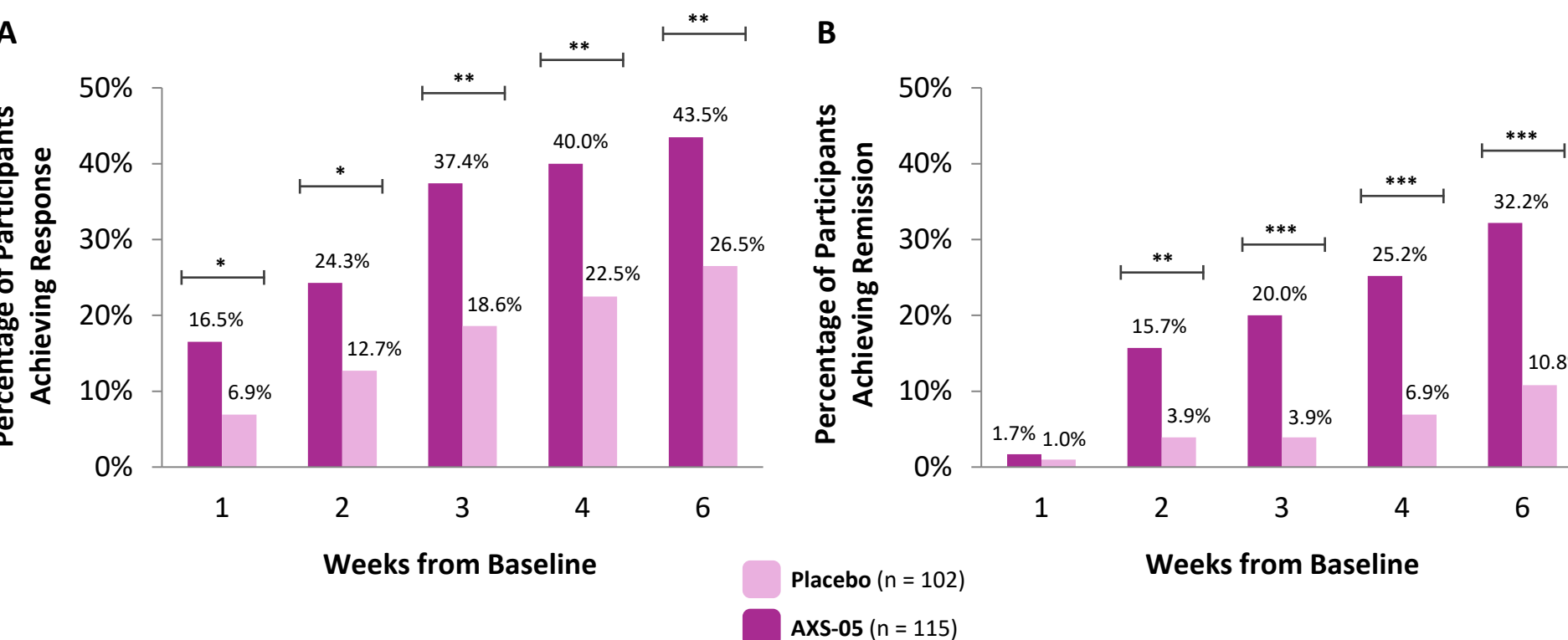
Figure 2: MADRS Total Score Change from Baseline Over Time



<sup>a</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P*  $\leq$  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

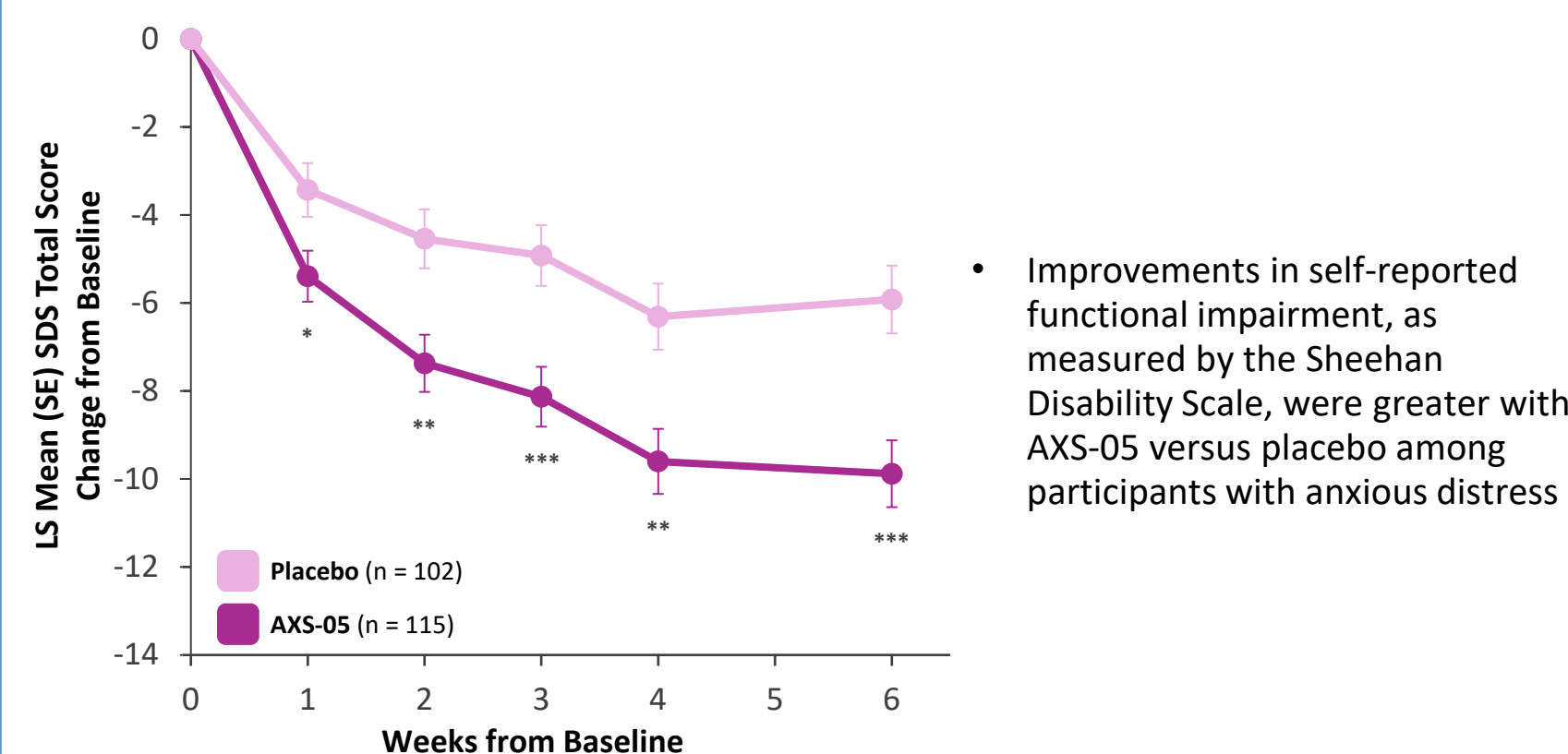
Figure 3: MADRS Response and Remission Among Participants with Anxious Distress



<sup>a</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P*  $\leq$  0.001; *P*-values are nominal. AXS-05, dextromethorphan-bupropion; MADRS, Montgomery-Åsberg Depression Rating Scale.

### SDS

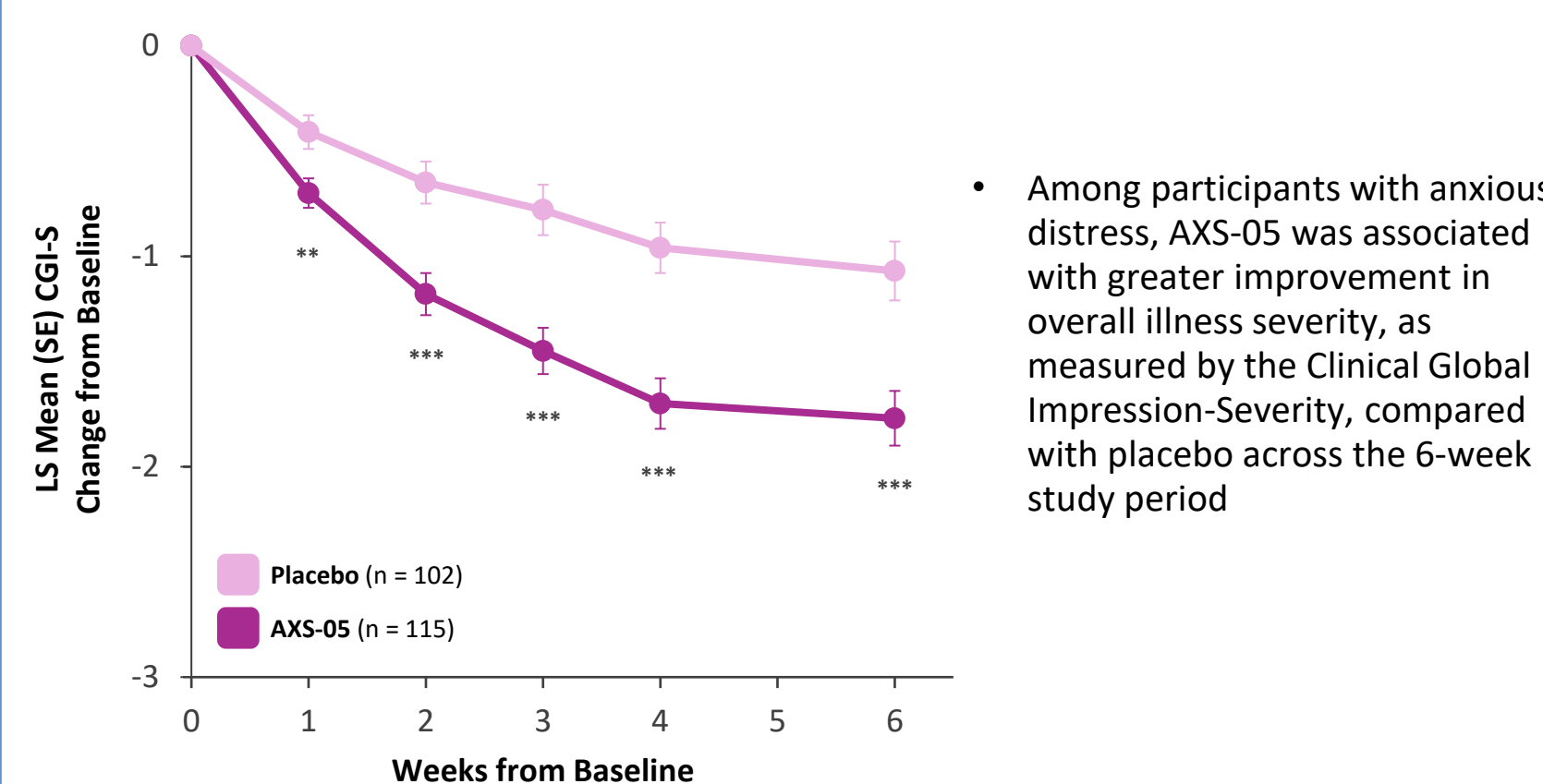
Figure 4: SDS Change from Baseline Among Participants with Anxious Distress



<sup>a</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P*  $\leq$  0.001; *P*-values are nominal. AXS-05, dextromethorphan-bupropion; LS, least squares; SDS, Sheehan Disability Scale; SE, standard error.

### CGI-S

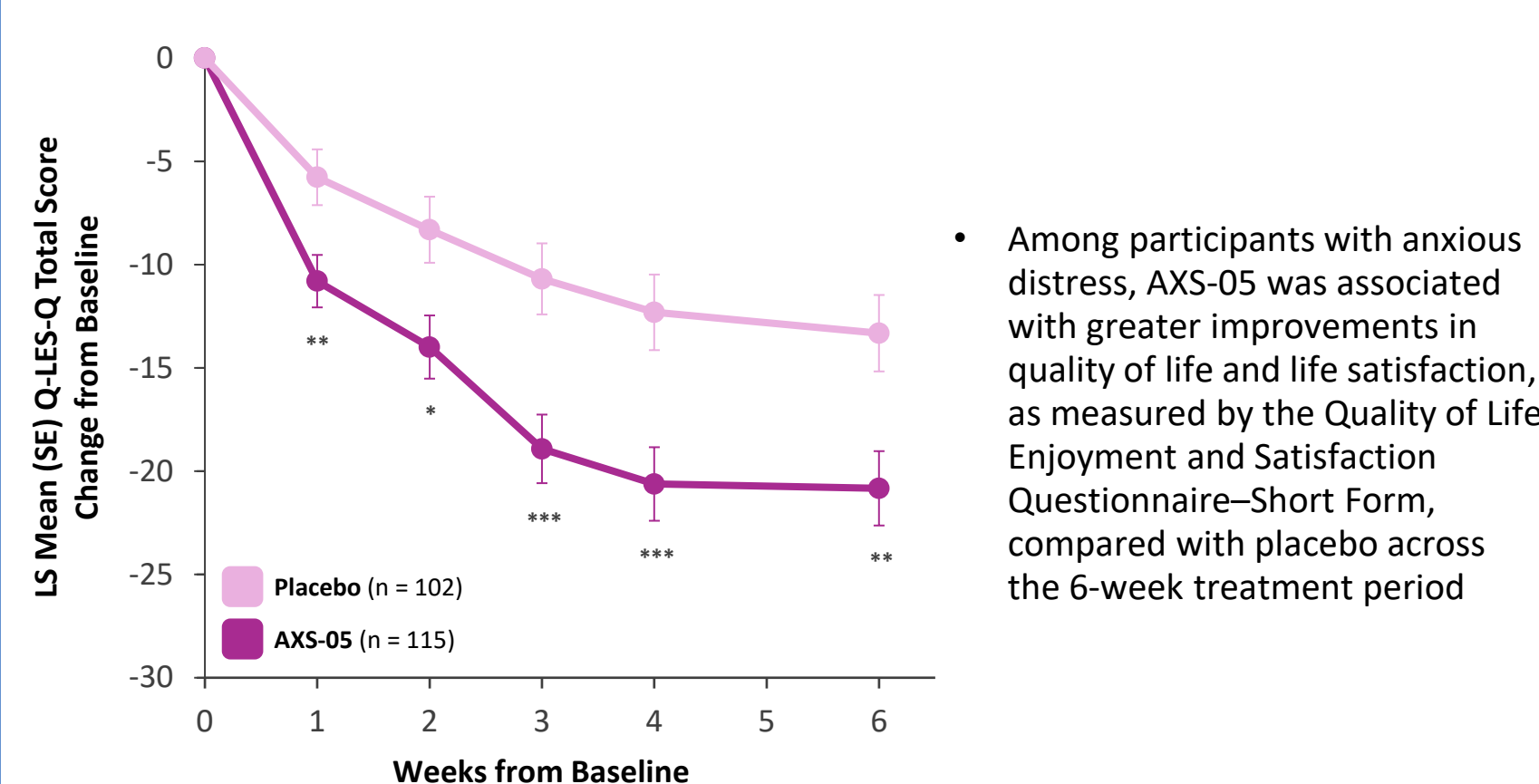
Figure 5: CGI-S Change from Baseline Among Participants with Anxious Distress



<sup>a</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P*  $\leq$  0.001; *P*-values are nominal. CGI-S, Clinical Global Impression-Severity; AXS-05, dextromethorphan-bupropion; LS, least squares; SE, standard error.

### Q-LES-Q-SF

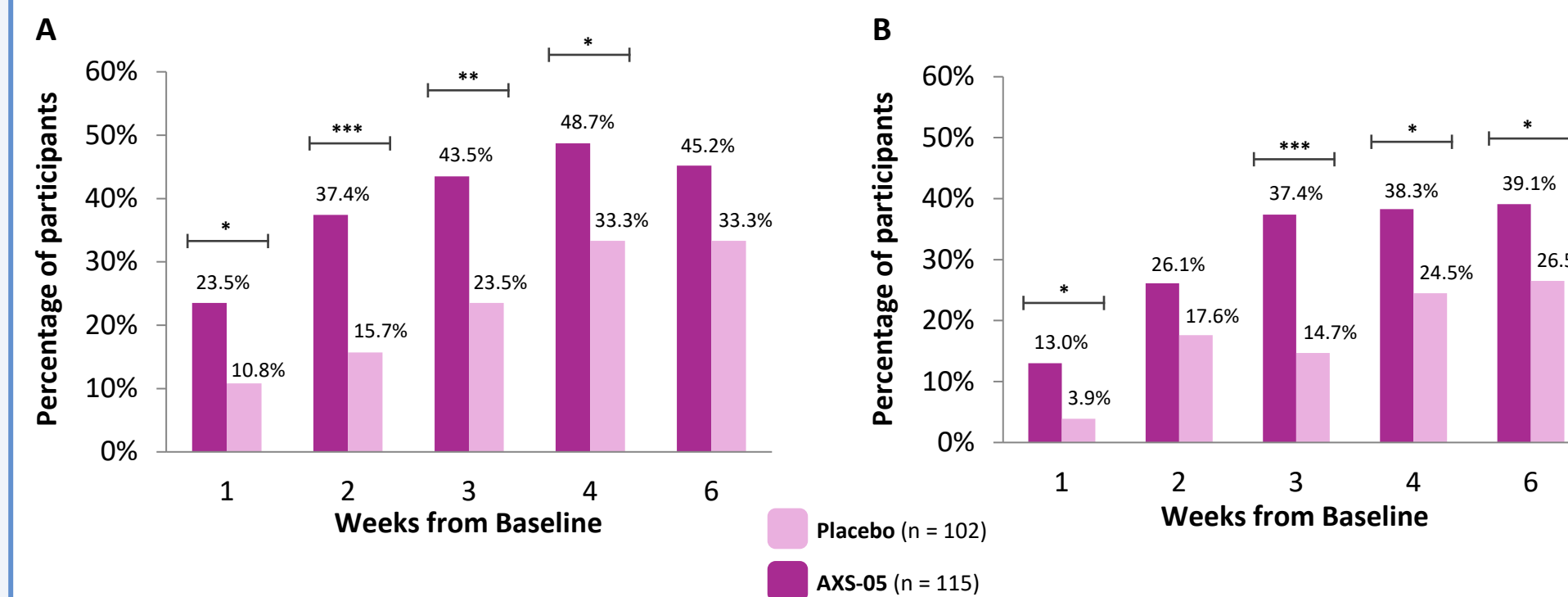
Figure 6: Q-LES-Q-SF Change from Baseline Among Participants with Anxious Distress



<sup>a</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P*  $\leq$  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<sup>a</sup>



<sup>a</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P*  $\leq$  0.001; *P*-values are nominal. <sup>b</sup>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

| Any Treatment-Emergent Adverse Event | Total                       |                              | Anxious Distress            |                              |
|--------------------------------------|-----------------------------|------------------------------|-----------------------------|------------------------------|
|                                      | AXS-05 (n=162) <sup>a</sup> | Placebo (n=164) <sup>a</sup> | AXS-05 (n=119) <sup>b</sup> | Placebo (n=103) <sup>b</sup> |
| 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%)

<sup>a</sup>Safety population: all subjects who received study drug.  
<sup>b</sup>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