Impact of AXS-05 (Dextromethorphan-Bupropion) on Patient-Reported Insomnia Symptoms: Results From the GEMINI Trial

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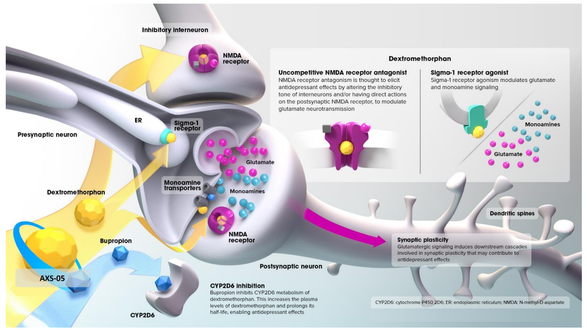
Introduction

- Insomnia is frequently reported among individuals with major depressive disorder (MDD)[1,2] and some antidepressants may worsen insomnia[3]
- In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, greater insomnia severity at baseline reduced the likelihood of achieving MDD remission, even after controlling for depression severity[4]
- In a survey of antidepressant-treated patients, more than 15% of patients reported that antidepressant-related insomnia was "extremely difficult to live with"[2]

AXS-05: A Novel, Oral NMDA Receptor Antagonist With Multimodal Activity



- AXS-05 [dextromethorphan-bupropion (Auvelity® extended-release tablet)] is a novel, oral, *N*-methyl-*D*-aspartate (NMDA) receptor antagonist with multimodal activity approved by the United States Food and Drug Administration for the treatment of MDD in adults[5]
  - The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist[5]
  - The bupropion component of AXS-05 is an aminoketone and CYP450 2D6 inhibitor, which serves primarily to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor[5]
- The efficacy and safety of AXS-05 in patients with MDD have been previously established[5-7]; however, specific effects on patient-reported insomnia have not yet been reported

Objective

- To assess the impact of AXS-05 compared with placebo on patient-reported insomnia symptoms in adults with MDD

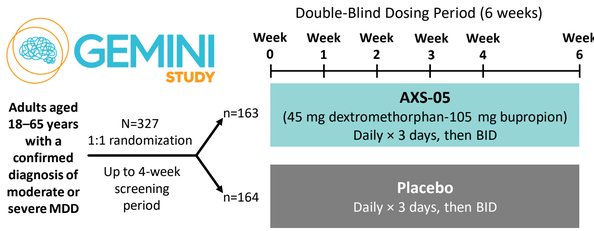
Methods

- GEMINI was a 6-week, randomized, double-blind, placebo-controlled trial (NCT04019704) conducted from June 20, 2019, to December 5, 2019, at 40 sites in the United States[6,8]

Key Inclusion / Exclusion Criteria	
Inclusion	**Exclusion**
▪ Adults aged 18–65 years ▪ DSM-5[9] criteria for MDD without psychotic features ▪ MADRS[10] total score ≥25 ▪ CGI-S[11] score ≥4 at baseline	▪ History of depressive episode with psychotic or catatonic features, treatment-resistant depression[a], schizophrenia, bipolar disorder, panic disorder, OCD, bulimia or anorexia nervosa, persistent neurocognitive disorder, or primary anxiety disorder ▪ Alcohol/substance use disorder within 1 year ▪ Clinically significant risk of suicide or harm to self or others ▪ Seizure disorder

[a]Defined as 2 or more failed prior treatments of adequate dose and duration in the current depressive episode.
CGI-S, Clinical Global Impression-Severity; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OCD, obsessive compulsive disorder.

Study Design



BID, twice daily; MDD, major depressive disorder.

- Current analysis: Post-hoc analysis of the impact of AXS-05 on patient-reported insomnia symptoms compared with placebo
- The Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16)[12] was assessed at baseline and weeks 1, 2, 3, 4, and 6
- The QIDS-SR-16 includes 3 insomnia-related items (falling asleep, sleeping during the night, waking up too early); scores on these items were combined into a single score ranging from 0–9
  - Baseline insomnia severity was categorized based on QIDS insomnia score: no insomnia (score ≤1), mild insomnia (score 2–5), and moderate–severe insomnia (score >5)
  - Outcomes for the current analyses included mean changes from baseline in QIDS insomnia score and response, which was defined as a ≥50% change from baseline in QIDS insomnia score
  - Data were analyzed for the modified intent-to-treat population, defined as all patients who were randomized, received ≥1 dose of the study drug, and had ≥1 post-baseline assessment. Changes from baseline were analyzed using a mixed model repeated measures method with treatment, week, and treatment-by-week interaction as factors; baseline value as a covariate; and subject as a random effect. Covariance structure was unstructured. Response rates were compared using a chi-square test
  - All *P* values are nominal

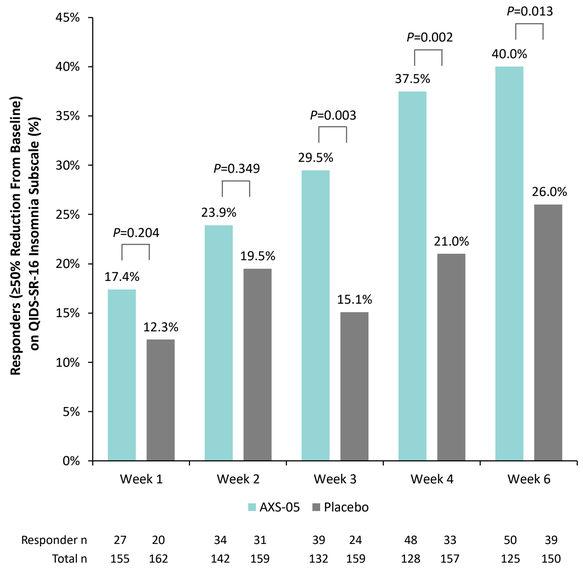
Results

Demographic and Baseline Characteristics[a]

Characteristic	AXS-05 (n=156)	Placebo (n=162)
Demographic characteristics		
Age, years, mean (SD)	42.1 (12.8)	41.2 (13.8)
Sex (female), n (%)	95 (60.9)	117 (72.2)
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	3 (1.9)	2 (1.2)
Other	2 (1.3)	6 (3.7)
BMI, kg/m^2, mean (SD)	29.3 (5.61)	29.3 (5.69)
Clinical characteristics		
MADRS total score[b], mean (SD)	33.6 (4.43)	33.2 (4.36)
CGI-S score[c], mean (SD)	4.6 (0.59)	4.6 (0.57)
QIDS-SR-16 score[d], mean (SD)	16.3 (3.79)	15.9 (4.05)
Insomnia characteristics		
QIDS-SR-16 insomnia subscale score, mean (SD)	5.9 (2.55)	5.3 (2.20)[e]
Insomnia severity category (QIDS-SR-16 insomnia subscale score), n (%)		
None (score ≤1)	8 (5.1)	7 (4.3)
Mild (score 2–5)	58 (37.2)	76 (46.9)
Moderate–severe (score >5)	90 (57.7)	78 (48.1)

[a]Modified intent-to-treat population. [b]MADRS scores range from 0–60, with higher scores indicating more severe depression. [c]CGI-S scores range from 1–7, with higher scores representing more severe disease. [d]QIDS-SR-16 scores range from 0–27, with higher scores indicating more severe depression. [e]n=161.
BMI, body mass index; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16, Quick Inventory of Depressive Symptomatology (Self-Report); SD, standard deviation.

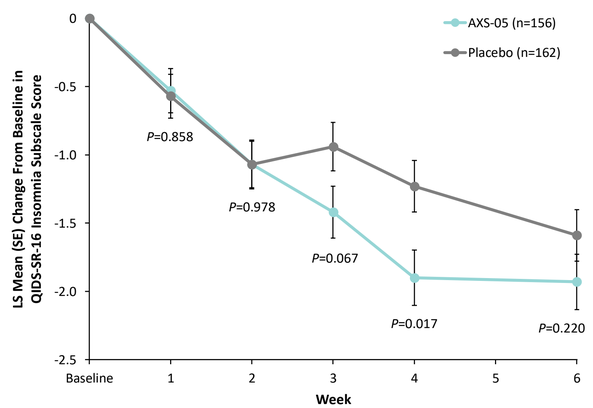
Rates of Response for QIDS-SR-16 Insomnia Subscale Score Were Higher for AXS-05 Compared With Placebo From Week 3 Through Week 6



	Week 1		Week 2		Week 3		Week 4		Week 6	
Responder n	27	20	34	31	39	24	48	33	50	39
Total n	155	162	142	159	132	159	128	157	125	150

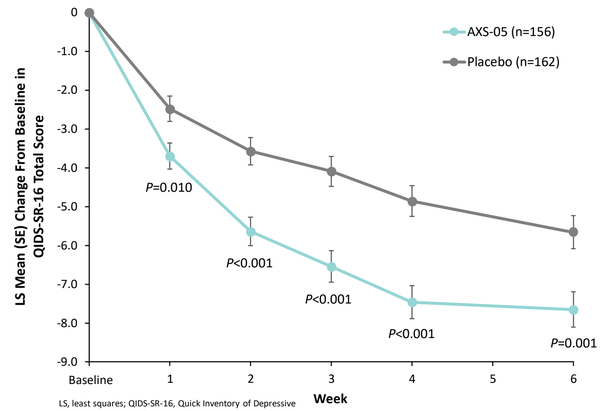
QIDS-SR-16, Quick Inventory of Depressive Symptomatology (Self-Report).

Change From Baseline for QIDS-SR-16 Insomnia Subscale Score Was Similar for AXS-05 and Placebo at Week 6



LS, least squares; QIDS-SR-16, Quick Inventory of Depressive Symptomatology (Self-Report); SE, standard error.

Change From Baseline in QIDS-SR-16 Total Score Was Significantly Greater With AXS-05 Compared With Placebo Beginning at Week 1



LS, least squares; QIDS-SR-16, Quick Inventory of Depressive Symptomatology (Self-Report); SE, standard error.

Safety and Tolerability

Adverse Events[a], n (%)	AXS-05 (n=162)	Placebo (n=164)
Dizziness	26 (16)	10 (6)
Headache	13 (8)	6 (4)
Diarrhea	11 (7)	5 (3)
Somnolence	11 (7)	5 (3)
Dry mouth	9 (6)	4 (2)
Sexual dysfunction[b]	9 (6)	0
Hyperhidrosis	8 (5)	0

[a]Includes adverse events occurring in ≥5% of AXS-05-treated patients and more than twice the rate of placebo. [b]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, and anorgasmia.

- Insomnia as an adverse event occurred in 4% of AXS-05-treated patients and 2% of placebo-treated patients
- 4% of patients treated with AXS-05 and 0% of patients treated with placebo discontinued the study due to an adverse reaction; no patients withdrew from the study due to insomnia

Conclusions

- In the GEMINI Study, patient-reported insomnia symptoms were common; on average, insomnia symptoms were moderate to severe at baseline
- Insomnia response rates were significantly greater with AXS-05 at week 3 and every time point thereafter
- These data provide additional evidence of the efficacy of AXS-05 on patient-centric outcomes in MDD

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