Efficacy, Tolerability, and Safety of AXS-05, a Novel Oral Antidepressant: Data from 3 Clinical Trials

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Key Question

- Does AXS-05 significantly improve depressive symptoms and remission compared to placebo and active controls?
- Are reductions in symptoms of depression and improvements in functioning and rates of remission durable over 12 months of treatment?

Conclusions

- AXS-05 (dextromethorphan-bupropion), a novel, oral NMDA receptor antagonist and sigma-1 receptor agonist approved for the treatment of MDD in adults, was evaluated in three clinical trials
  - AXS-05 rapidly and statistically significantly improved depressive symptoms at Weeks 1 and 2 in placebo and active controlled trials (GEMINI and ASCEND, respectively)
  - In both studies, remission from depressive symptoms was achieved by Week 2 and maintained over the 6-week treatment period
- Rapid and substantial reduction in symptoms of depression and improvement in functioning with AXS-05 were durable over 12 months of treatment
- AXS-05 was well-tolerated and the safety profile of AXS-05 over the 12-month COMET trial was consistent with the short-term trials with no new safety signals detected

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Disclosures

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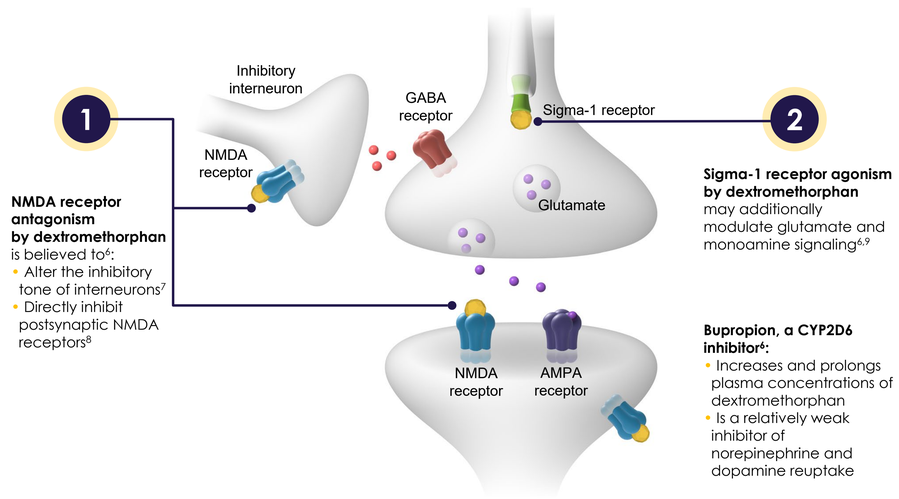
Introduction

- Major depressive disorder (MDD) is a highly prevalent, chronic, disabling disorder and a leading cause of suicide[1,2]
- Currently approved oral antidepressants act primarily via monoaminergic mechanisms and are associated with low remission rates, prolonged time to response, and adverse events (AEs) impacting treatment success and adherence[3,4]
- Clinical and preclinical evidence has implicated dysfunctional glutamatergic neurotransmission in the pathophysiology of MDD, suggesting a role for NMDA receptor antagonism in the treatment of MDD[1,5]

AXS-05: A Novel, Oral NMDA Receptor Antagonist

- AXS-05 (dextromethorphan-bupropion) is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and monoamine modulator approved by the US Food and Drug Administration for the treatment of MDD in adults (**Figure 1**)[6]
  - Dextromethorphan is an antagonist of the NMDA receptor and a sigma-1 receptor agonist[6]
  - Bupropion is an aminoketone and cytochrome P450 2D6 inhibitor that increases the bioavailability of dextromethorphan[6]

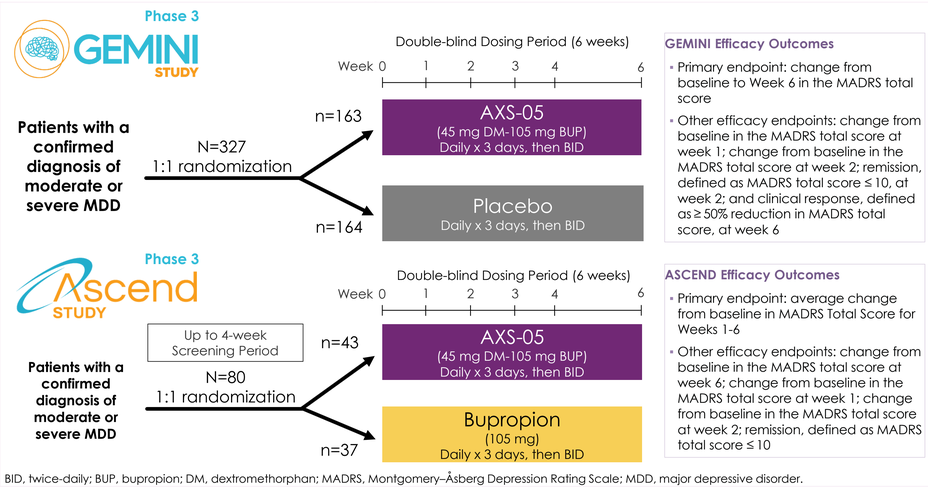
Figure 1. AXS-05 Mechanism of Action



Methods & Study Design

GEMINI and ASCEND

- The ASCEND phase 2 and GEMINI pivotal phase 3 trials assessed efficacy, tolerability, and safety of AXS-05 vs placebo or active comparator bupropion (BUP 105 mg), respectively, in patients with moderate to severe major depressive disorder[10,11]



BID, twice-daily; BUP, bupropion; DM, dextromethorphan; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder.

Table 1. GEMINI and ASCEND Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
▪ Male or female 18-65 years of age ▪ Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for current major depressive disorder without psychotic features ▪ MADRS total score of ≥25 ▪ Clinical Global Impressions-Severity score of ≥4 at baseline	▪ History of depressive episode with psychotic or catatonic features, treatment-resistant depression (defined as 2 or more failed prior treatments of adequate dose and duration in the current depressive episode), schizophrenia, bipolar disorder, panic disorder, obsessive convulsive disorder, 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 ▪ Concomitant psychotropic medication

COMET

- The COMET trial was a Phase 3, single arm, open label U.S. trial where 876 patients (including 611 newly enrolled patients and 265 patients completing a prior AXS-05 study) were treated with AXS-05 twice daily
- The primary endpoint was long-term safety as measured by the incidence of treatment-emergent adverse events (TEAEs)
- Additional exclusion criteria for newly enrolled patients include history of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or experimental central nervous system treatment during the current episode or within 6 months

Key Findings

Patient Population

- Demographics were similar across both AXS-05 and control groups for all 3 trials (**Table 2**)

Table 2. Demographics and Baseline Characteristics

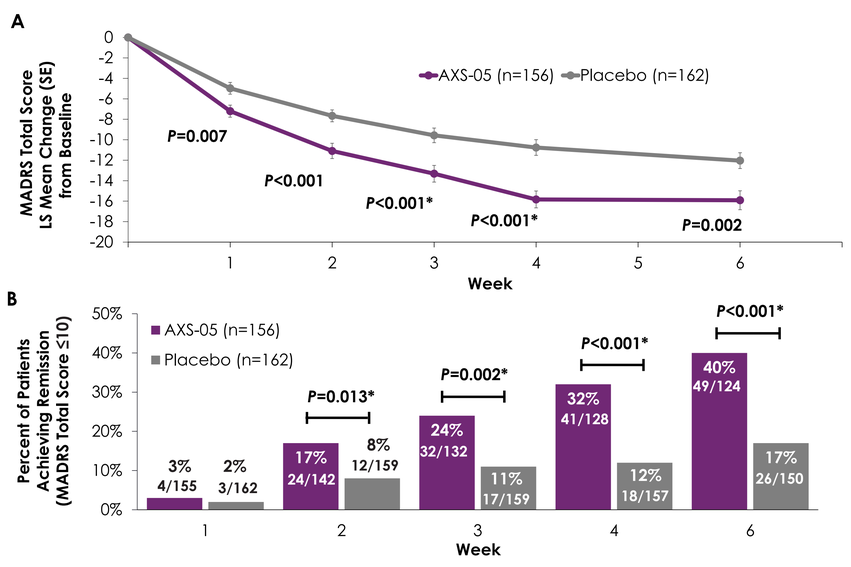
	GEMINI		ASCEND		COMET
	AXS-05 n=156	Placebo n=162	AXS-05 n=43	Bupropion n=37	AXS-05 n=876
Age, years	42.1 (12.80)	41.2 (13.77)	37.3 (12)	37.7 (11.9)	42.5 (13.5)
Female Gender, n (%)	95 (60.9)	117 (72.2)	25 (58.1)	26 (70.3)	560 (63.9)
Race, n (%)					
White	84 (53.8)	92 (56.8)	30 (69.8)	20 (54.1)	509 (58.1)
Black or African American	58 (37.2)	54 (33.3)	12 (27.9)	14 (37.8)	301 (34.4)
Asian	9 (5.8)	8 (4.9)	1 (2.3)	0	29 (3.3)
Other	2 (1.3)	6 (3.7)	0	3 (8.1)	-
BMI, kg/m²	29.3 (5.61)	29.3 (5.69)	6 (14.0)	11 (29.7)	30.9 (7.11)
MADRS Total Score	33.6 (4.43)	33.2 (4.36)	31.8 (4.0)	32.2 (4.5)	32.7 (4.64)
CGI-S Score	4.6 (0.59)	4.6 (0.57)	4.4 (0.6)	4.5 (0.5)	4.5 (0.61)

Data are mean (SD) unless otherwise stated.
CGI-S, Clinical Global Impression – Severity scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

GEMINI Efficacy

- MADRS (Montgomery–Åsberg Depression Rating Scale) change from baseline to Week 6 was significantly greater for AXS-05 vs placebo (-15.9 vs -12.0; least-squares mean difference=-3.87; *P*=0.002). MADRS scores were significantly improved from baseline vs placebo at each week (**Figure 2A**)
- MADRS remission rates were significantly greater with AXS-05 from Weeks 2-6 (Week 6: 39.5% vs 17.3%; *P*<0.001; **Figure 2B**)

Figure 2. A. Improvement in MADRS Total Score† ; B. Clinical Remission (MADRS Total Scores ≤10)††

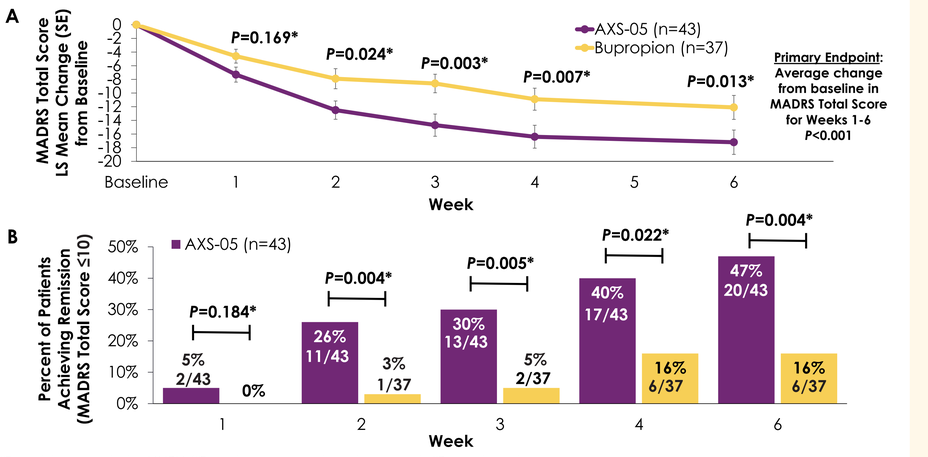


†Endpoints analyzed using MMRM; ††Endpoints analyzed via χ^2 tests; *P-value is nominal.

ASCEND Efficacy

- Mean change from baseline in MADRS score over Weeks 1–6 was significantly greater for AXS-05 vs BUP (-13.7 vs -8.8; LSMD=-4.9; *P*<0.001). Statistically significant MADRS total score improvement from baseline for AXS-05 vs BUP occurred from Week 2 to trial end (Week 6: -17.3 vs. -12.1; least-squares mean difference=-5.2; P=0.013; **Figure 2A**)
- Remission rates were significantly greater with AXS-05 from Week 2 to 6 (all *P*≤0.022; **Figure 2B**)

Figure 3. A. MADRS Total Scores†; B. Remission (MADRS Total Score ≤10)††



†Endpoints analyzed using MMRM; ††Endpoints analyzed using chi-square tests; *P-value is nominal.

COMET Efficacy

- Patients who received open-label AXS-05 twice daily demonstrated MADRS total score improvement over 12 months
- MADRS response and remission rates were improved from baseline at all timepoints
- Improvements from baseline were also observed in Clinician Global Impression of Improvement and Sheehan Disability Scale scores

Safety

Table 3. Summary of Adverse Events in Randomized Controlled Trials

	GEMINI		ASCEND	
	AXS-05 n=162	Placebo n=164	AXS-05 n=48	Bupropion n=48
Any adverse event, n (%)	100 (61.7)	74 (45.1)	35 (72.9)	31 (64.6)
Serious adverse events, n (%)	1 (0.6)	0	0	0
Severe adverse events, n (%)	1 (0.6)	2 (1.2)	3 (6.3)	1 (2.1)
Adverse event leading to discontinuation of study drug, n (%)	10 (6.2)	1 (0.6)	6 (12.5)	6 (12.5)

- The most commonly reported adverse reactions in the pivotal GEMINI trial (≥5% and twice the rate of placebo) with AXS-05 were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis[6]
- The safety profile of AXS-05 in ASCEND and COMET were consistent with GEMINI, with no new safety signals detected