Impact of AXS-05, an Oral NMDA Receptor Antagonist, on Anhedonic Symptoms in Major Depressive Disorder

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Key Question

- Does AXS-05 improve anhedonic symptoms in MDD compared to placebo as assessed by the MADRS anhedonia subscale?

Conclusions

- AXS-05, a novel oral NMDA receptor antagonist, rapidly and statistically significantly improved anhedonic symptoms, as well as overall depressive symptoms
- Significant improvements in anhedonic symptoms with AXS-05 treatment were observed at Week 1 and at every timepoint thereafter
- AXS-05 was well tolerated
- These data support the efficacy of AXS-05 in a broad range of symptomatology in patients with MDD

References

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Disclosures

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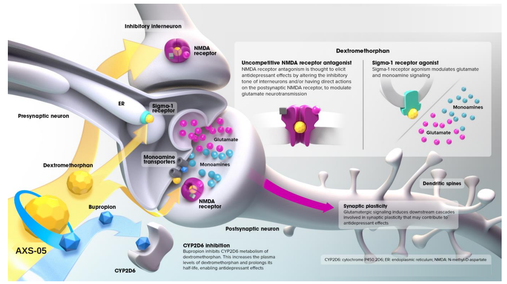
Introduction

- **Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling, prevalent, biologically-based disorder, and a leading cause of suicide[1,2]
- **MDD is difficult to treat:** 63% of MDD patients experience an inadequate response to current first-line oral therapies (STAR*D trial results), and the majority of these inadequate responders also fail second-line treatment (69%)[3]
- Anhedonia, the inability to feel pleasure, is one of the core features of major depressive disorder (MDD) and is present in up to 75% of individuals diagnosed with MDD[4]
- Anhedonia is considered among the most bothersome aspects of MDD by patients, has been associated with decreased functioning and is a risk factor for non-response to antidepressant therapy [5,6]
- **Response to treatment takes time:** Current oral antidepressants are associated with prolonged time to clinically meaningful response (up to 6-8 weeks)[3]
- **Need for mechanistically novel approaches:** Currently approved oral antidepressants work primarily through monoaminergic mechanisms[7]
- **Glutamatergic** hypothesis of MDD: 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[1,7]
- **There is an urgent clinical need for:** New, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments[1]

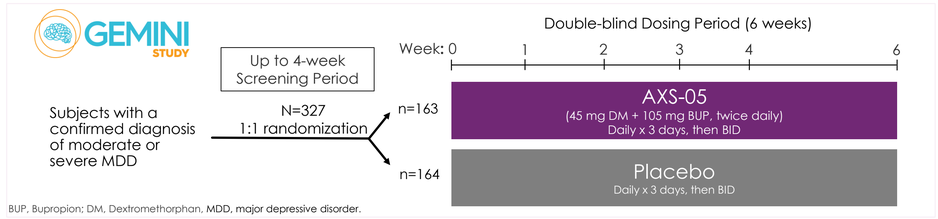
AXS-05: A Novel, Oral NMDA Receptor Antagonist

- 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**)[8]
  - Dextromethorphan is an antagonist of the NMDA receptor and a sigma-1 receptor agonist[8]
  - Bupropion is an aminoketone and cytochrome P450 2D6 inhibitor that increases the bioavailability of dextromethorphan[8]

Figure 1. AXS-05 mechanism of action



Methods & Study Design



BUP, Bupropion; DM, Dextromethorphan, MDD, major depressive disorder.

Primary Endpoint: Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6

Key Secondary Endpoints: Change from baseline and in MADRS at Week 1 and Week 2

- A *post-hoc* analysis was conducted to determine the impact of AXS-05 as compared to placebo on the 5-item MADRS anhedonia subscale
- Previous research has demonstrated that the MADRS anhedonia subscale is highly correlated to the to the Snaith-Hamilton Pleasure Scale, a validated measure of hedonic tone[9]

MADRS Anhedonia Subscale: : Change from baseline and rate of response as measured by the **MADRS Anhedonia Subscale** which includes 5-items:

- Apparent sadness
- Reported sadness
- Concentration difficulties
- Lassitude
- Inability to feel

Table 1. Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
▪ Male or female 18-65 years of age ▪ DSM-5 criteria for current MDD without psychotic features ▪ MADRS total score of ≥ 25 ▪ CGI-S score of ≥ 4 at baseline	▪ History of depressive episode with psychotic or catatonic features, treatment-resistant depression, 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

CGI-S, Clinical Global Impression – Severity scale; DSM-5, The Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; MADRS, Montgomery–Åsberg Depression Rating Scale; SE, standard error; TMS, transcranial magnetic stimulation.

Key Findings

Patient Population

- Baseline disease severity represents a moderate-to-severely depressed population (**Table 2**)
- Demographics were similar across both AXS-05 and control groups (**Table 2**)

Table 2. Demographics and Baseline Characteristics

	AXS-05 (n=156)	Placebo (n=162)
Age	42.1 (12.71)	41.1 (13.78)
Female gender, n (%)	98 (60.1%)	117 (71.3%)
Race, n (%)		
White	88 (54.0)	92 (56.1)
Black or African American	61 (37.4)	55 (33.5)
MADRS total score	33.6 (4.43)	33.2 (4.36)
MADRS Anhedonia score	19.8 (2.48)	19.6 (2.40)
CGI-S Score	4.6 (0.59)	4.6 (0.57)

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

Primary Analysis

- AXS-05 achieved the primary endpoint – statistically significant reduction from baseline on the MADRS total score at week 6 (-16.6 vs. -11.9; *P*=0.002), compared to placebo (**Figure 2**)
- AXS-05 rapidly and statistically significantly reduced MADRS total score compared to placebo, by week 1, the first timepoint measured (*P*=0.007), at week 2 (*P*<0.001), and at all timepoints thereafter (**Figure 2 and Table 3**)

Figure 2. Improvement in symptoms of depression (MADRS Total) with AXS-05 compared to placebo

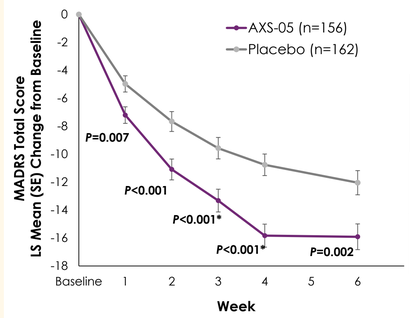


Table 3. Key Secondary Endpoints

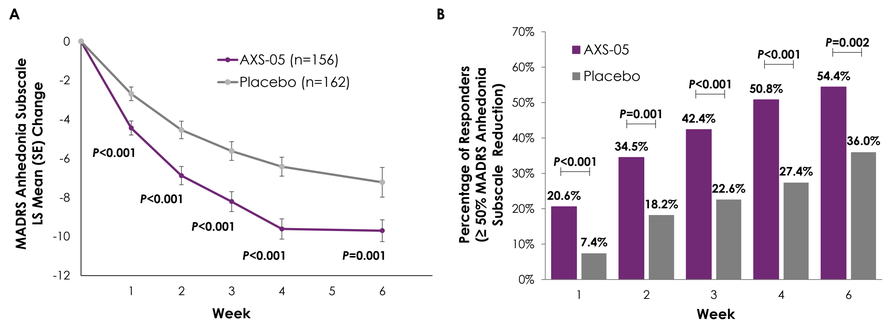
	AXS-05 (n=156)	Placebo (n=162)	Difference	*P*-value
Change in MADRS Total Score at Week 1	-7.2	-5.0	-2.2	0.007
Change in MADRS Total Score at Week 2	-11.1	-7.7	-3.4	<0.001

*P-values are nominal and based on chi square mean test.
P-value based on the difference in LS Means between AXS-05 and Placebo groups.
MADRS, Montgomery–Åsberg Depression Rating Scale; SE, standard error.

Anhedonia

- At Week 1 (the first timepoint measured) treatment with AXS-05 resulted in a statistically significant mean reduction from baseline in the MADRS anhedonia subscale score of 4.44, versus 2.69 points for placebo (*P*<0.001; **Figure 3A**)
- By Week 6, the mean reduction from baseline in the MADRS anhedonia subscale was 9.70 for AXS-05 compared to 7.22 for placebo (*P*=0.001; **Figure 3A**)
- Rates of response (≥ 50% MADRS anhedonia subscale improvement) were statistically significantly greater for AXS-05 compared to placebo at Week 1 (*P*<0.001) and at every timepoint thereafter (**Figure 3B**)
- Response was achieved by 54% of AXS-05 patients versus 36% of placebo patients at Week 6 (*P*=0.002; **Figure 3B**)

Figure 3. Improvement in anhedonia with AXS-05 compared to placebo (A) and response (≥ 50% reduction) in MADRS anhedonia subscale (B)



P-value based on the difference in LS Means between AXS-05 and Placebo groups.
MADRS, Montgomery–Åsberg Depression Rating Scale; SE, standard error.

Safety

Table 4. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients Treated with AXS-05

	AXS-05 (n=162)	Placebo (n=164)
Any Treatment-Emergent Adverse Event, %	62	45
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction[a]	6	0
Hyperhidrosis	5	0

[a]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, and anorgasmia.

- The most commonly reported adverse events were dizziness, nausea, and headache (**Table 4**)
- Rates of discontinuation due to adverse events were 4% for AXS-05 and 0%, for placebo