Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder: Results of a Phase 2, Double-Blind, Active-Controlled Trial

ASCP 2019 Oral Session

AXSOME THERAPEUTICS

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New Agents Needed for Treatment of MDD

- Major depressive disorder (MDD) is a disabling, chronic and prevalent condition.[1] MDD is the leading cause of suicide in the U.S.[2]
- 63% and 44% of MDD patients have inadequate response to initial therapy and second line therapy, respectively.[1]
- Current antidepressants are associated with a high rate of inadequate response (as much as 70%), and prolonged time to clinically meaningful response (up to 6-8 weeks).[1]
- All currently approved oral MDD agents work primarily through monoaminergic mechanisms.[3]

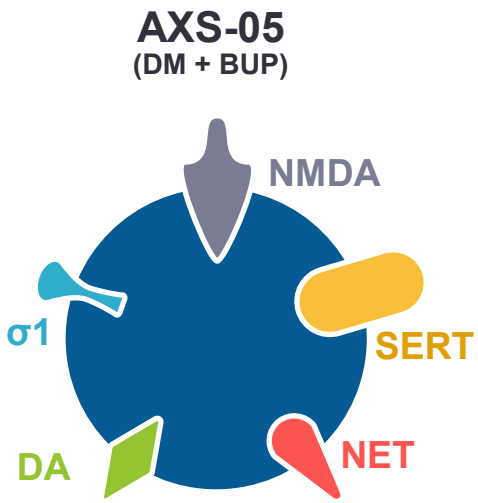
[1]Rush AJ, et al. *Am J Psychiatry.* 2006; 11(163):1905-1917.
[2]Kadriu B, et al. *Int J Neuropsychopharmacol.* 2019;22(2):119-135.
[3]Machado-Vieira R, et al. *Prog Neurobiol.* 2017;152:21-37.

Glutamatergic Signaling in MDD: Potential Role for NMDA Blockade

- 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.[1,2]
- NMDA receptor blockade may result in improved antidepressant response and faster onset of action.[1,2]
- Activation of AMPA receptors induced by NMDA receptor blockade induces downstream cascades involved in neural plasticity that may underlie antidepressant-like effects.[3,4,5]

[1]Kadriu B, et al. *Int J Neuropsychopharmacol.* 2019;22(2):119-135.
[2]Machado-Vieira R, et al. *Prog Neurobiol.* 2017;152:21-37.
[3]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[4]Zarate Niciu MJ, et al. *J Neural Transm (Vienna).* 2014;121(8):907-924.
[5]Freudenberg F, et al. *Neurosci Biobehav.* Rev. 2015;52:193-206.

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



BUP = Bupropion; DA = Dopamine; DM = Dextromethorphan; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate; SERT= Serotonin Reuptake Transporter; σ1 = Sigma-1 Receptor

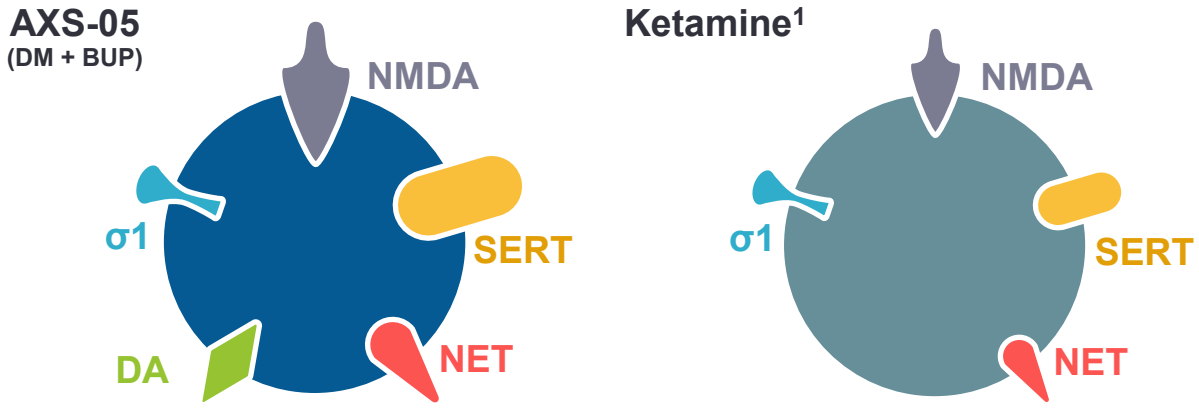
- ***NMDA receptor antagonism*** – DM component of AXS-05
- ***Sigma-1 receptor agonism*** – DM component of AXS-05
- ***Triple-reuptake inhibition*** *(serotonin, norepinephrine, dopamine)* – DM and bupropion components of AXS-05
- ***Modulation of DM plasma concentrations*** – Bupropion component of AXS-05 increases DM concentrations into potentially therapeutic range.

- AXS-05 (dextromethorphan and bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.[1]

[1]Kadriu B, et al. *Int J Neuropsychopharmacol.* 2019;22(2):119-135.

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

Comparison of Receptor Binding and Activity for AXS-05 and Ketamine



	DM	Ketamine	Assay
NMDA receptor binding (IC_{50})	402 nM	1047 nM	• Rat cerebellar granule neurons[2]
Sigma-1 agonist activity (K_i)	150 nM	140 μM	• Rat cerebellum[3] or PC12 cells[4]
Serotonin reuptake inhibition (K_i)	23 nM	162 μM	• Rat brain synaptosomes[5] • Human kidney cells[6]
Norepinephrine reuptake inhibition (K_i)	240 nM	67 μM	• Rat brain synaptosomes[5] • Human kidney cells[6]

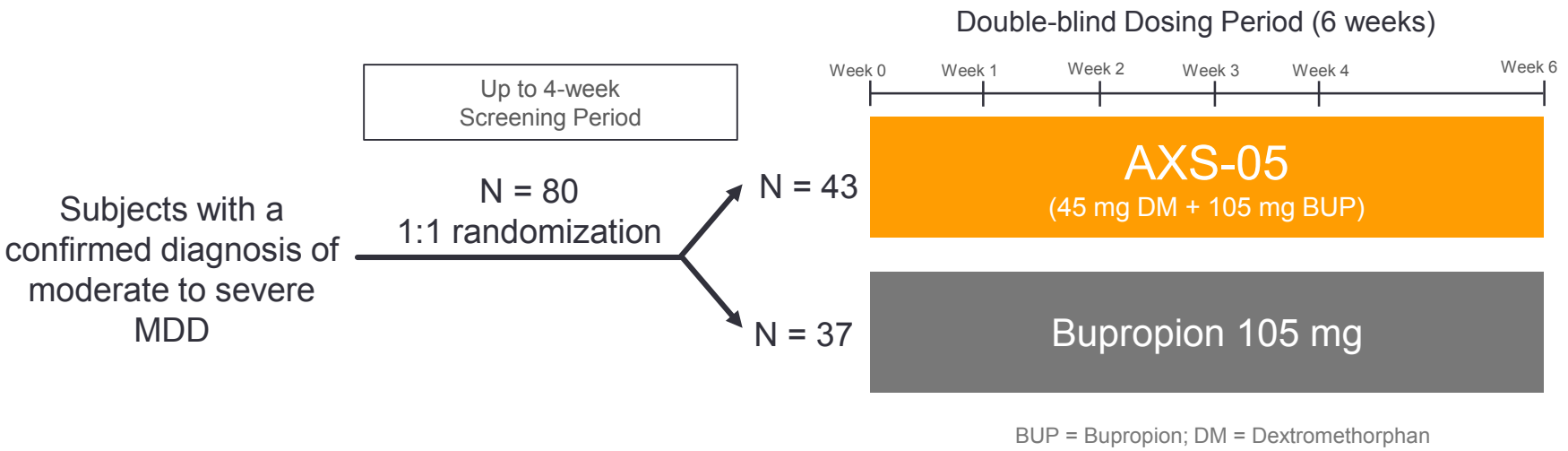
Analysis courtesy of Dr. Stephen M. Stahl

[1] Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013. [2] Berman FW, et al. *J Biochem Toxicol*. 1996;11(5):217-226. [3] Werling LL, et al. *Exp Neurol*. 2007;207(2):248-257. [4] Robson MJ, et al. *Eur Neuropsychopharmacol*. 2012;22(4):308-317. [5] Taylor CP, et al. *Pharmacol Ther*. 2016;164:170-182. [6] Nishimura M, et al. *Anesthesiology*.1998;88(3):768-774.

Abbreviations: BUP = Bupropion; DA = Dopamine; DM = Dextromethorphan; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate; SERT= Serotonin Reuptake Transporter; σ1 = Sigma-1 Receptor

ASCEND Trial of AXS-05 in MDD: Design Summary

ASCEND (Assessing Clinical Episodes in Depression) Trial



BUP = Bupropion; DM = Dextromethorphan

- Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial
- Primary Endpoint: Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score over the 6-week treatment period (calculated at each time point and averaged)
- Extensive quality control measures

ASCEND Trial of AXS-05 in MDD: Key Entry Criteria

Inclusion criteria included:

- Male or female 18-65 years of age inclusive
- DSM-5 criteria for current MDD without psychotic features
- Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥ 25
- CGI-S score of ≥ 4 at baseline

Exclusion criteria included:

- History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current episode or in the past 6 months
- Schizophrenia, bipolar disorder, obsessive compulsive disorder
- Psychiatric symptoms secondary to any other general medical condition

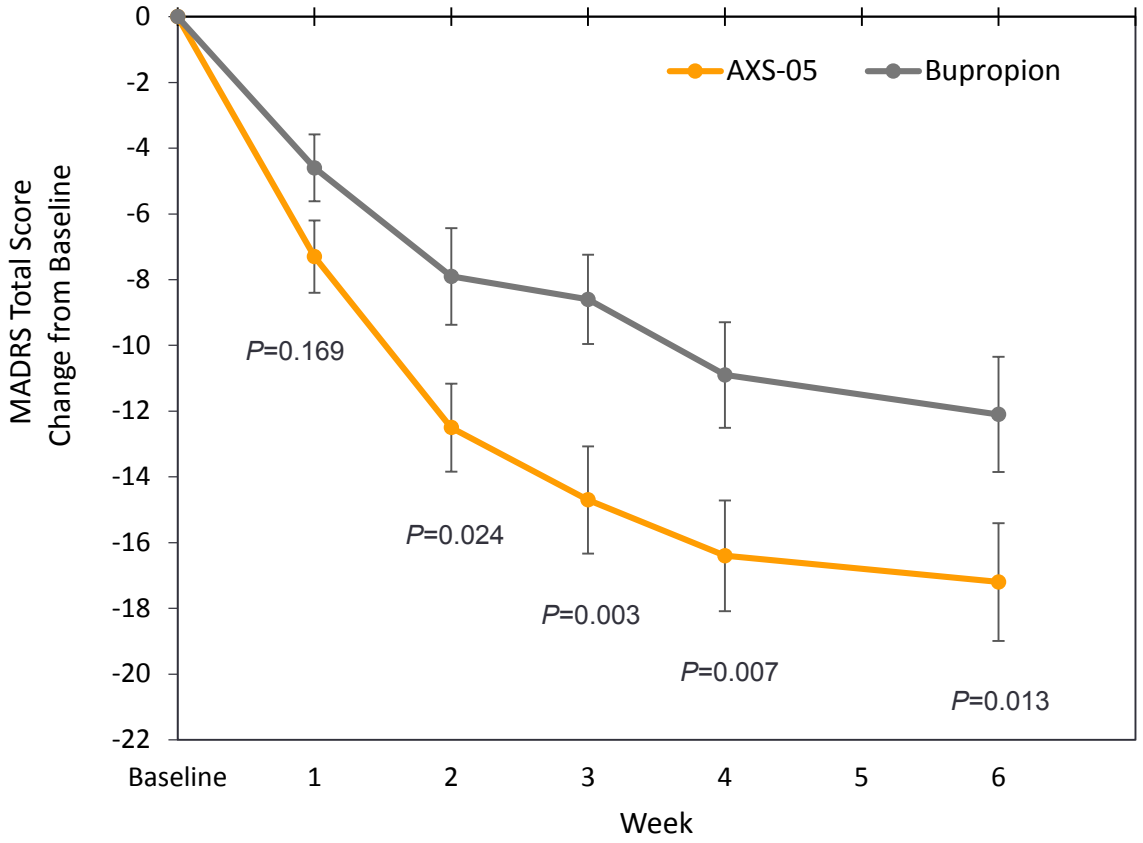
ASCEND Trial of AXS-05 in MDD: Demographics and Baseline Characteristics

	AXS-05 (45 mg DM / 105 mg BUP) (n = 43)	Bupropion (105 mg) (n = 37)
Demographics		
Age (years)	37.3 (11.94)	37.7 (11.85)
Female Gender, n (%)	25 (58.1%)	26 (70.3%)
Race, n (%)		
White	30 (69.8%)	20 (54.1%)
Black or African American	12 (27.9%)	14 (37.8%)
Asian	1 (2.3%)	0
Other	0	3 (8.1%)
≥ 3 Previous Depressive Episodes, n (%)	22 (51.2%)	19 (51.3%)
Baseline Clinical Characteristics		
MADRS Total Score	31.8 (4.04)	32.2 (4.46)
CGI-S Score	4.4 (0.50)	4.5 (0.51)
MADRS-6 Subscale Score	21.5 (2.42)	21.5 (2.97)

Data are mean (SD) unless otherwise stated.
BUP = bupropion; CGI-S = Clinical Global Impression – Severity; DM = dextromethorphan; MADRS = Montgomery-Åsberg Depression Rating Scale

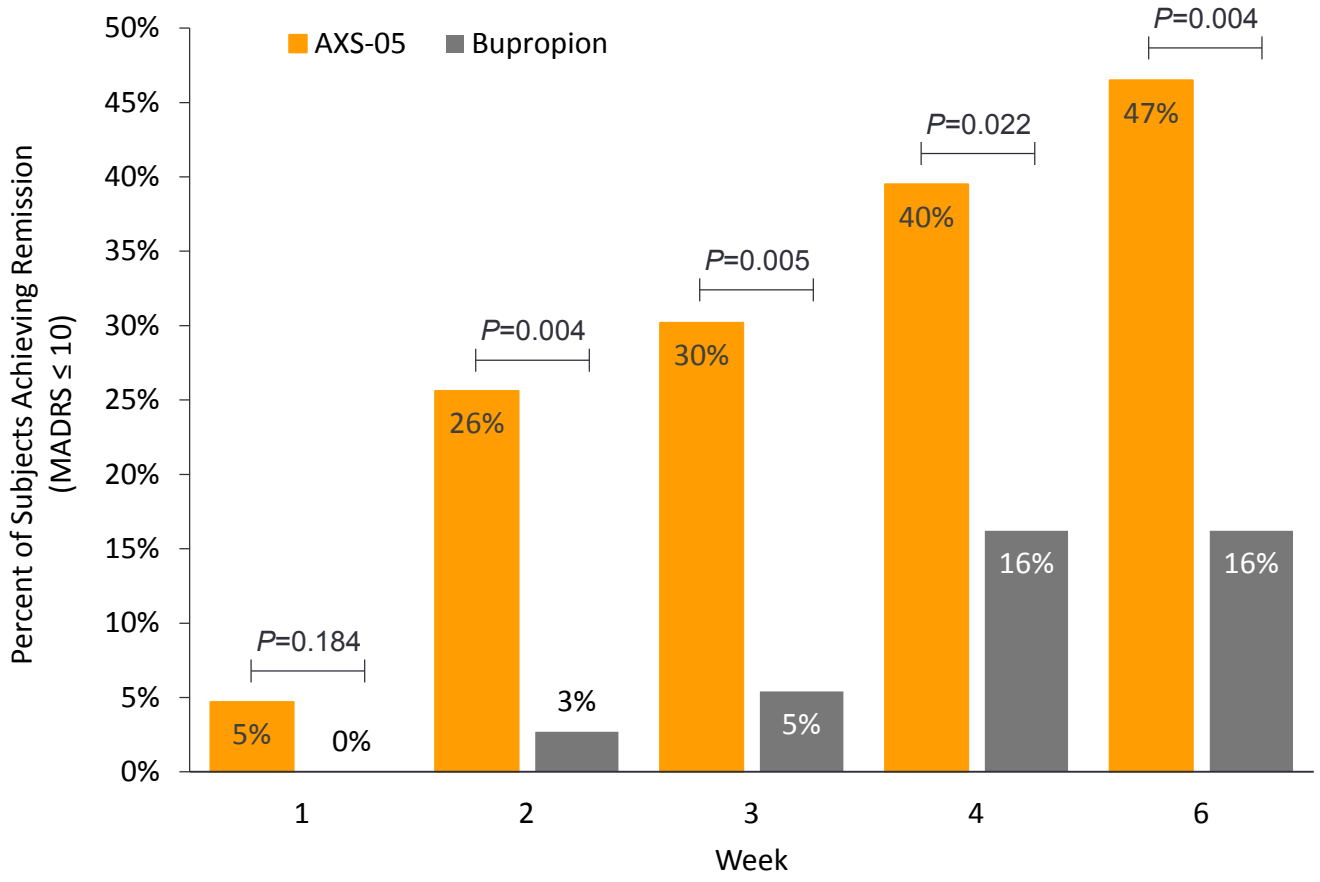
- Demographics and baseline clinical characteristics were similar across both treatment groups.
- 23% of subjects had received prior first line treatment in their current major depressive episode.
- Study completion rates were >70% in both treatment groups.

Improvement in MADRS Total Score with AXS-05: Primary Endpoint



	AXS-05	Bupropion	P-Value
Primary Endpoint			
Change in MADRS Total Score over 6-Week Period (averaged)	-13.7	-8.8	< 0.001
Change in MADRS Total Score at Week 6	-17.2	-12.1	0.013

Early and Sustained Remission with AXS-05: MADRS ≤ 10



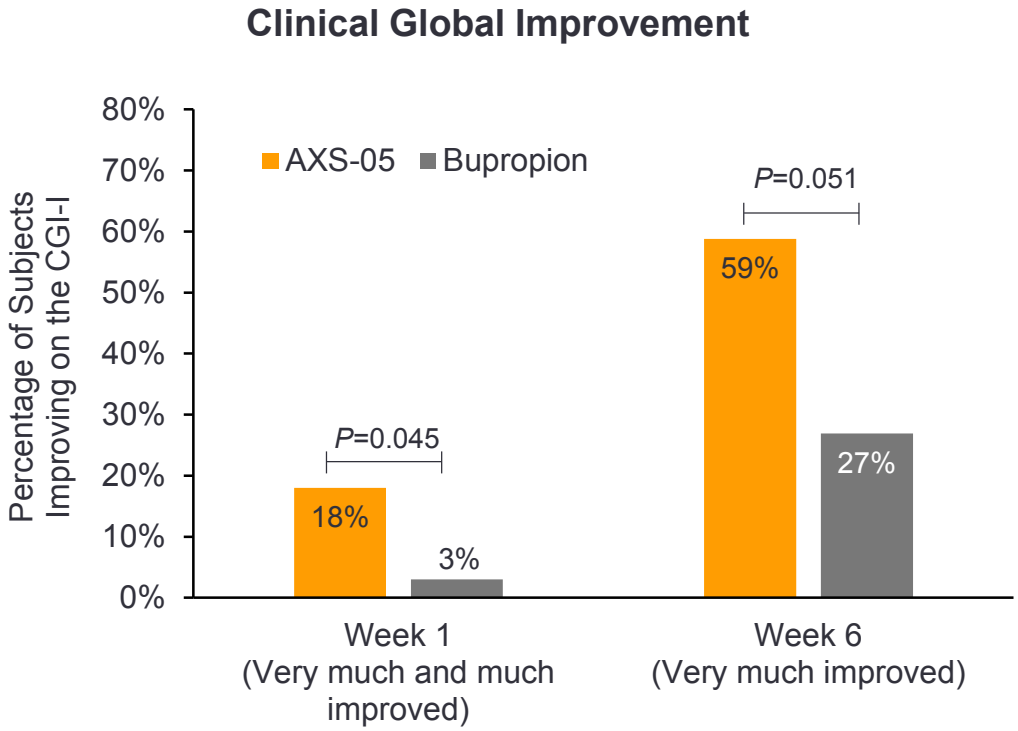
Improvement in MADRS-6 with AXS-05: Core Symptoms of Depression

P-values over Time for Improvement of AXS-05 over Bupropion on MADRS-6	
Study Week	**P-value**
Week 1	0.162
Week 2	0.027
Week 3	0.003
Week 4	0.008
Week 6	0.007

- The MADRS-6 is the sum of six of the 10 MADRS items that have been described as the core symptoms of depression.[1,2]
- AXS-05 significantly improved the core symptoms of depression, as measured by the MADRS-6, versus bupropion, demonstrating a 12.58 point reduction in the MADRS-6 subscale compared to an 8.70 point reduction for bupropion at Week 6 (p=0.007).
- AXS-05 rapidly improved the core symptoms of depression as compared to bupropion, demonstrating numerical superiority as early as Week 1, and achieving statistical significance at Week 2 (p=0.027) and at every time point thereafter.

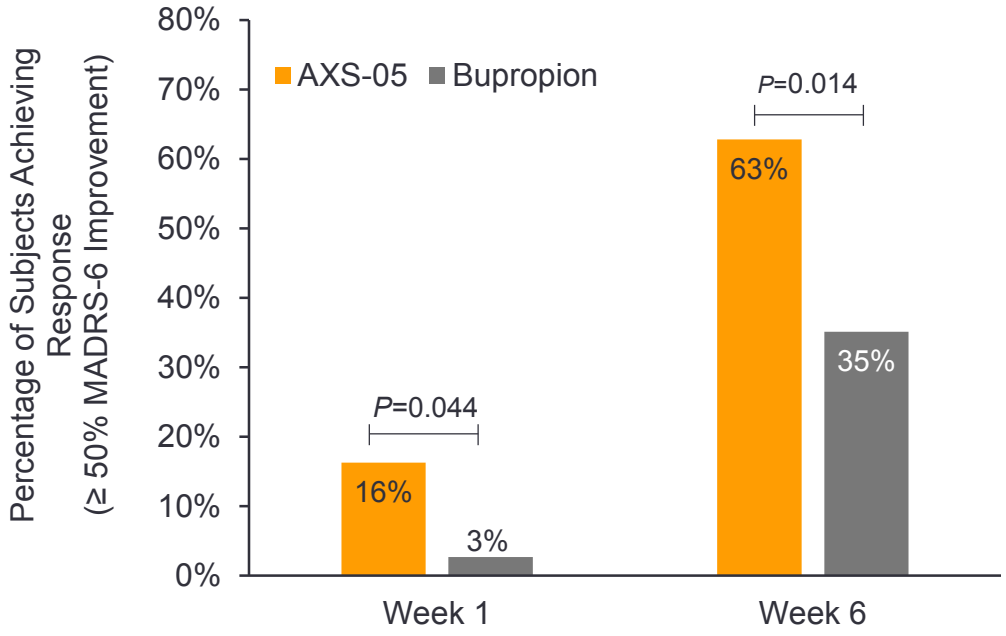
[1] Thase et al. *Int J Psychiatry Clin Pract.* 2012 Jun;16(2):121-31. [2] Bech P. *Dialogues Clin Neurosci.* 2006;8(2):207-15

Rapid and Sustained Effect with AXS-05: Clinical Global Improvement



- As early as Week 1, AXS-05 treatment resulted in a statistically significantly greater proportion of subjects who were much or very much improved, as measured by the CGI-I, as compared to bupropion (p=0.045).
- The improvement over bupropion was maintained at Week 6 with 59% of patients treated with AXS-05 very much improved compared to 27% of those treated with bupropion (p=0.051).

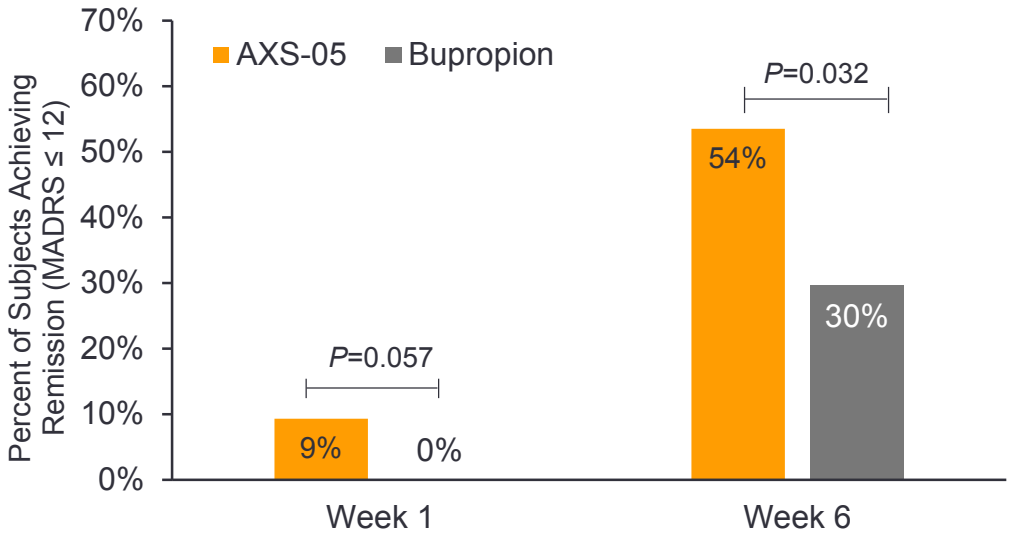
Rapid and Sustained Effect with AXS-05: Clinical Response on MADRS-6 (≥ 50% improvement)



- As early as Week 1, AXS-05 resulted in a statistically significantly greater rate of clinical response on the MADRS-6 (≥ 50% improvement) as compared to bupropion (p=0.044).
- Statistical significance maintained at Week 6 (response rates of 63% for AXS-05 and 35% for bupropion, p=0.014).

Rapid and Sustained Effect with AXS-05: Remission (MADRS ≤ 12)

Achievement of Remission Using MADRS Total Score ≤ 12



- Remission may be defined by a MADRS total score of ≤ 12 (prespecified secondary endpoint).
- As early Week 1, 9% of patients treated with AXS-05 achieved remission versus no patients treated with bupropion (p=0.057).
- Rates of remission after 6 weeks of treatment were statistically significantly greater with AXS-05 than with bupropion (54% vs. 30%, p=0.032).

ASCEND Trial Results:
Safety & Tolerability

- AXS-05 was safe and well tolerated in this trial with similar overall rates of adverse events being reported in both treatment arms.
- There were no reported serious adverse events.
- The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite and anxiety.
- The rate of discontinuations due to adverse events was approximately 12% for each treatment group.
- Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

ASCEND Trial of AXS-05 in MDD: Conclusions

- AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, representing a potential mechanistically new approach for the treatment of depression.
- Treatment with AXS-05 in this trial resulted in rapid, substantial, and statistically significant improvement in depressive symptoms in patients with MDD.
- AXS-05 met the primary endpoint demonstrating statistically significant improvements on the MADRS total score versus the active comparator bupropion.
- Rapid antidepressant effects were seen as early as Week 1 (earliest assessment) and sustained through Week 6.
- Statistically significant effects for AXS-05 as compared to bupropion were observed on multiple secondary endpoints including MADRS-6, CGI-I, CGI-S, remission, and clinical response.
- AXS-05 was safe, well tolerated, and not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.
- The novel mechanism of action of AXS-05 was associated with a differentiated clinical profile as compared to currently approved agents for MDD.

Q&A