

# Rapid Effects of AXS-05, an Oral NMDA Receptor Antagonist, in Major Depressive Disorder: Results from Two Randomized, Double-Blind, Controlled Trials



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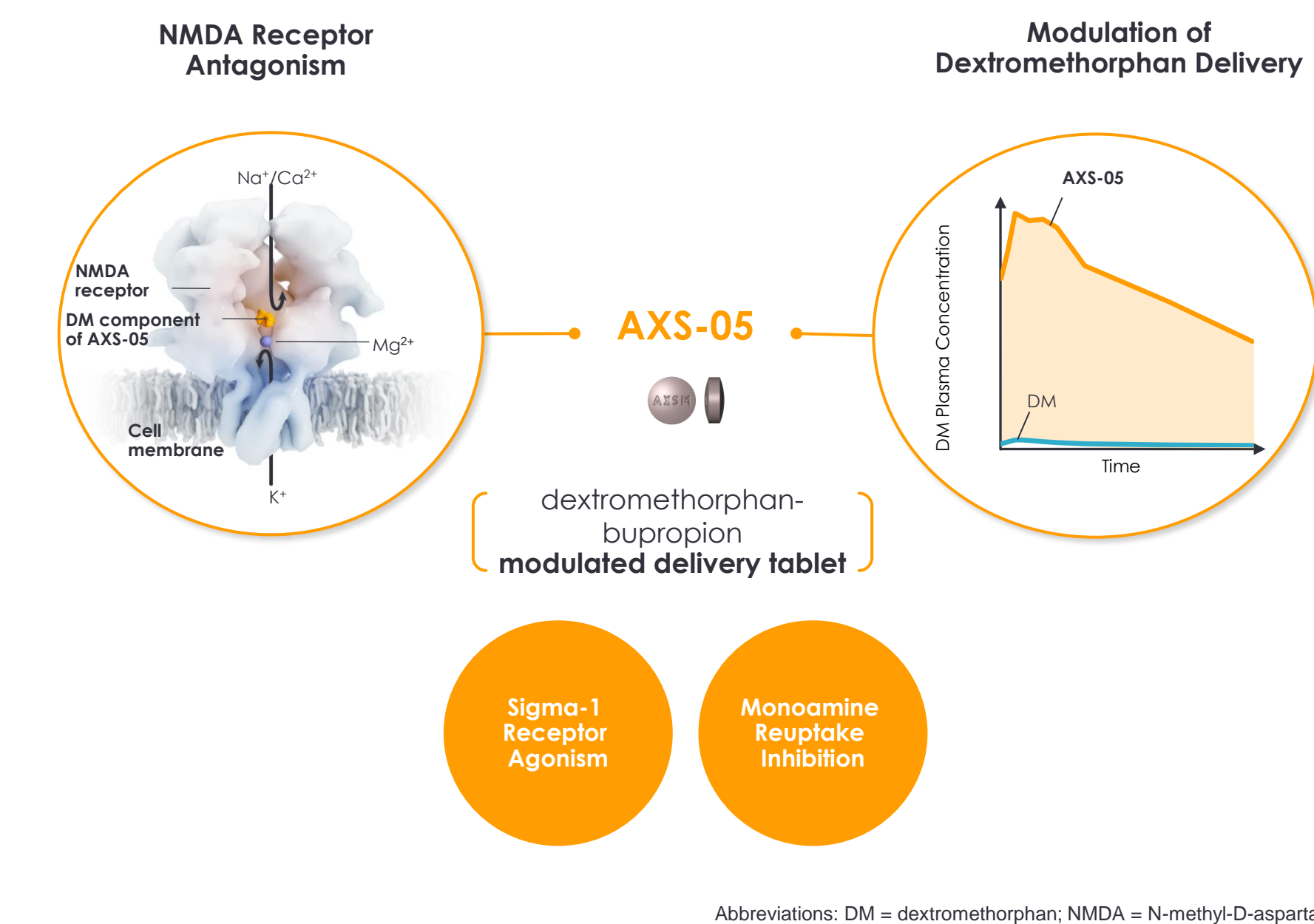
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## Introduction

- Major depressive disorder (MDD) is a serious disorder:** MDD is a chronic, disabling, prevalent, and life-threatening, biologically-based disorder, and a leading cause of suicide<sup>1,2</sup>
- 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%)<sup>3</sup>
- Response to treatment takes time:** Current oral antidepressants are associated with prolonged time to clinically meaningful response (up to 6-8 weeks)<sup>3</sup>
- Delayed antidepressant treatment response** is associated with an increased risk of relapse, poorer long-term outcomes, and a decreased likelihood of functional improvement<sup>3-5</sup>
- Need for mechanistically novel approaches:** Currently approved oral antidepressants work primarily through monoaminergic mechanisms<sup>6</sup>
- There is an urgent clinical need for:** New, more effective, faster-acting, mechanistically novel, and well-tolerated MDD treatments<sup>1,2</sup>
- In this research:** Herein we analyze data from two randomized controlled trials to determine the effect of AXS-05, a novel, oral, investigational, NMDA receptor antagonist, on symptoms of MDD during the first 2 weeks of treatments

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



### AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity:<sup>1,7</sup>

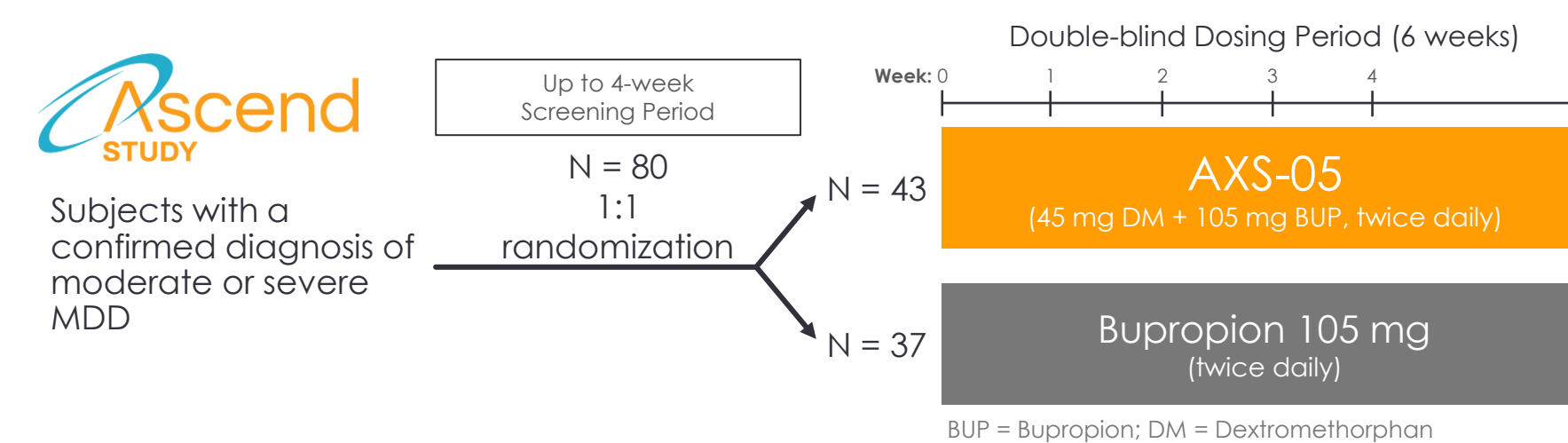
- The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist<sup>7</sup>
- These actions modulate glutamatergic neurotransmission
- The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor<sup>7</sup>

## References

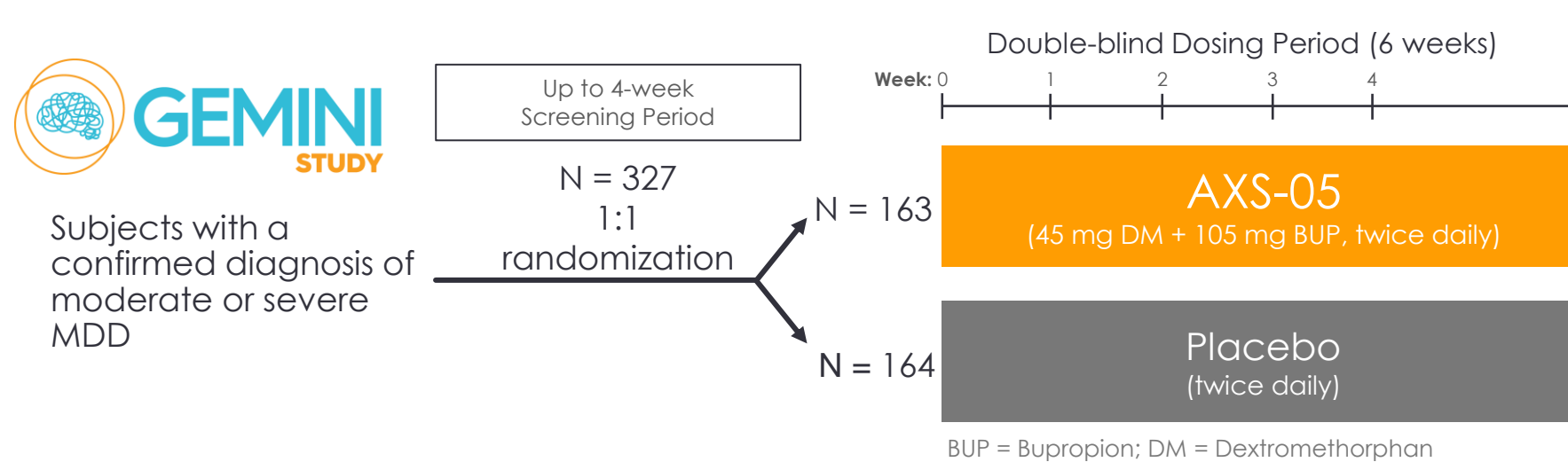
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## Trial Objectives and Designs

- The objective of the ASCEND Phase 2 trial was to evaluate the efficacy and safety of AXS-05, as compared to the active comparator bupropion, in patients with moderate or severe MDD



- The objective of the GEMINI Phase 3 trial was to evaluate the efficacy and safety of AXS-05 as compared to placebo in patients with moderate or severe MDD



### Key Inclusion and Exclusion Criteria for ASCEND and GEMINI

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>Male or female, 18-65 years of age</li> <li>DSM-5 criteria for current MDD without psychotic features</li> <li>MADRS total score of <math>\geq 25</math></li> <li>CGI-S score of <math>\geq 4</math> at baseline</li> </ul>	<ul style="list-style-type: none"> <li>History ECT, vagus nerve stimulation, TMS or any experimental central nervous system treatment during the current episode or in the past 6 months</li> <li>Schizophrenia, bipolar disorder, obsessive compulsive disorder</li> <li>Psychiatric symptoms secondary to any other general medical condition</li> </ul>

### Demographics and Baseline Characteristics

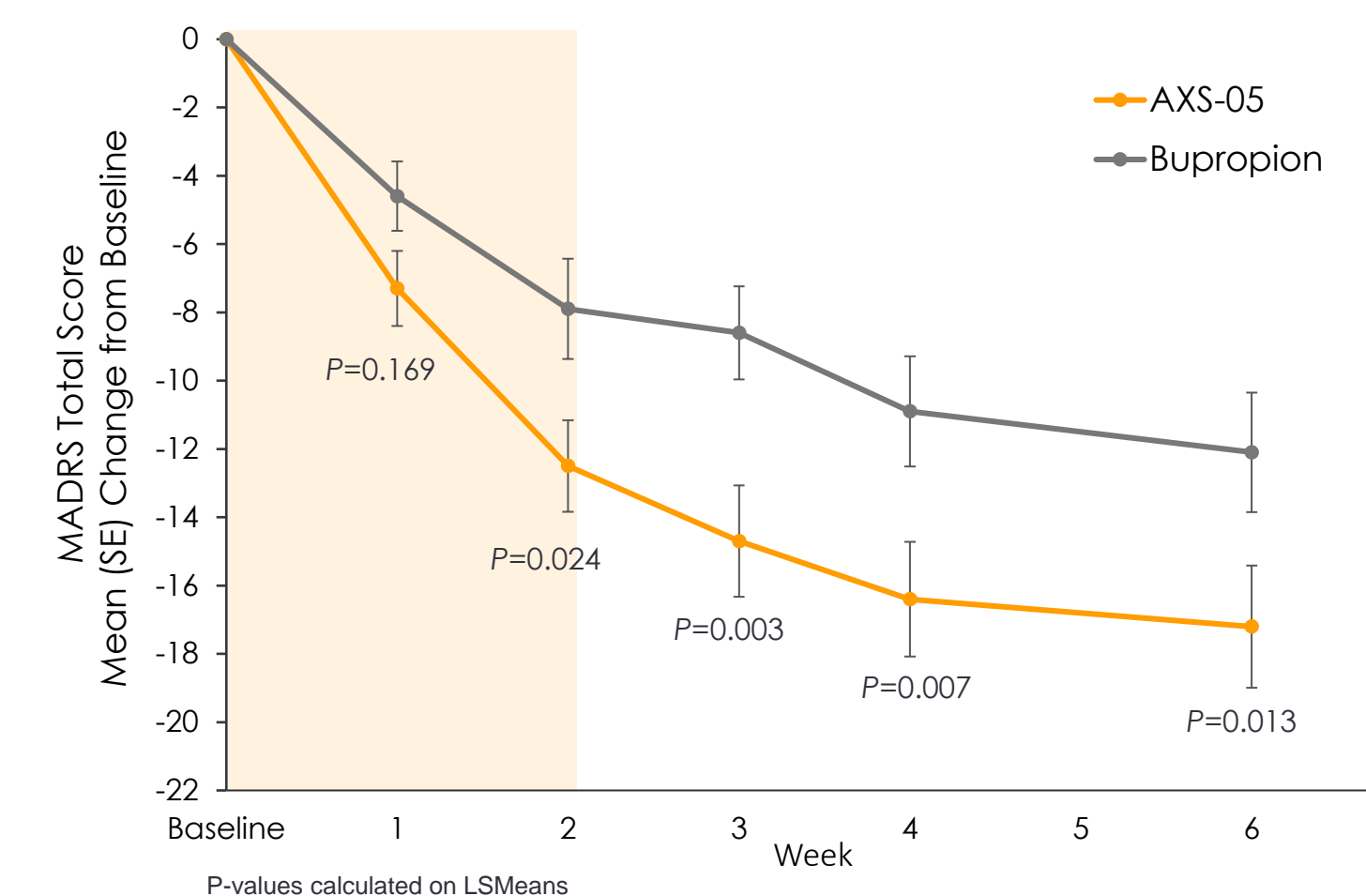
	GEMINI		ASCEND	
	AXS-05	Placebo	AXS-05	Bupropion
<b>Demographics</b>				
Age (years)	42.1 (12.71)	41.1 (13.78)	37.3 (11.94)	37.7 (11.85)
Female gender, n (%)	98 (60.1%)	117 (71.3%)	25 (58.1%)	26 (70.3%)
<b>Race, n (%)</b>				
White	88 (54.0%)	92 (56.1%)	30 (69.8%)	20 (54.1%)
Black or African American	61 (37.4%)	55 (33.5%)	12 (27.9%)	14 (37.8%)
<b>Clinical Characteristics</b>				
MADRS total score	33.6 (4.43)	33.2 (4.36)	31.8 (4.04)	32.2 (4.46)
CGI-S Score	4.6 (0.59)	4.6 (0.57)	4.4 (0.50)	4.5 (0.51)
SDS total score	20.3 (5.96)	19.3 (5.82)	SDS was not assessed in ASCEND	
Q-LES-Q-SF total score (% maximum)	34 (13.46)	36 (12.29)	Q-LES-Q-SF was not assessed in ASCEND	

Data are mean (SD) unless otherwise stated. SDS = Sheehan Disability Scale. Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

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

## Results

### Improvement in Symptoms of Depression with AXS-05 Compared to Bupropion (ASCEND)

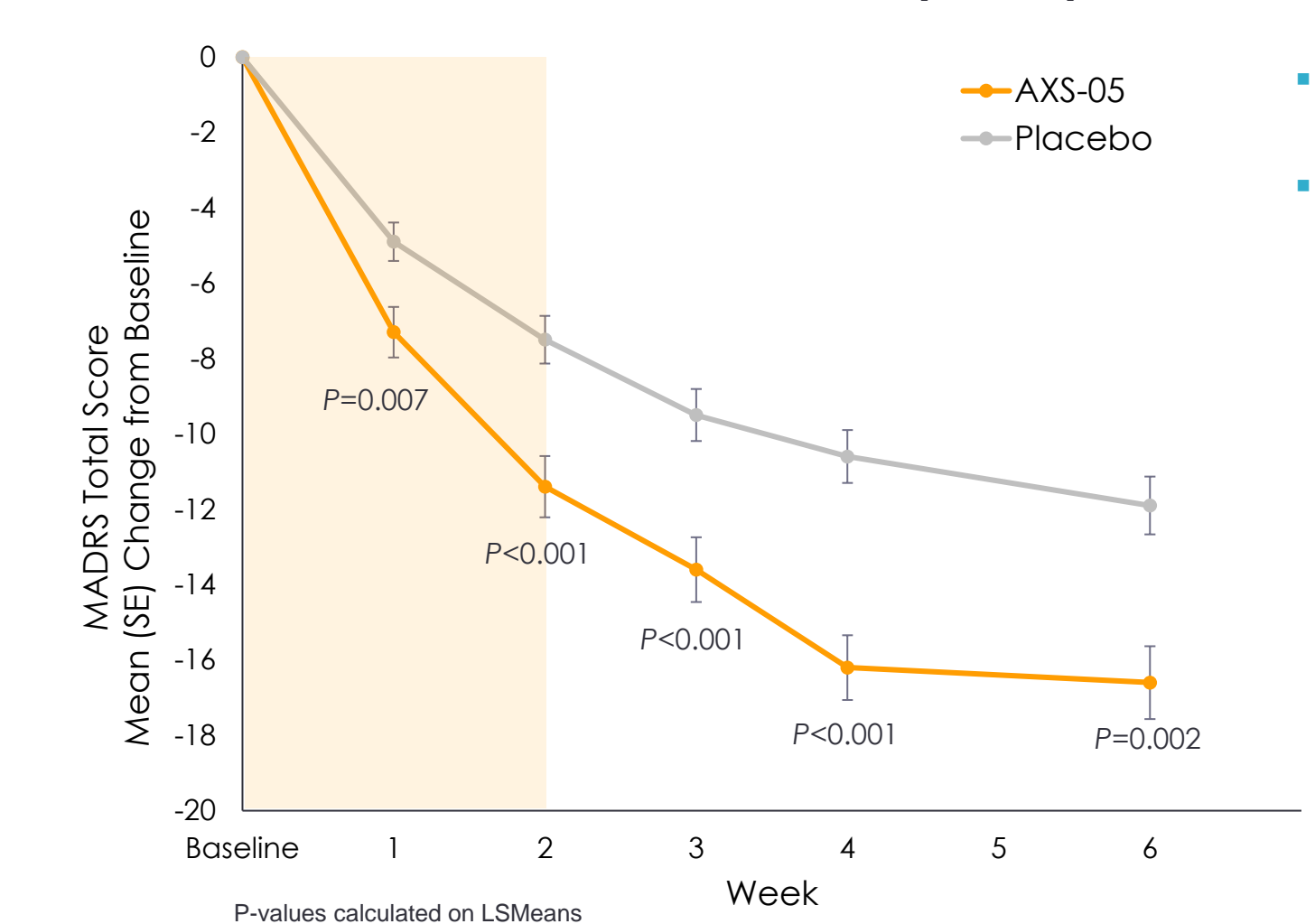


- AXS-05 achieved the primary endpoint ( $p < 0.001$ )
- AXS-05 demonstrated rapid reduction in depressive symptoms with numerical superiority to bupropion as early as Week 1, and statistically significant superiority at Week 2 and all timepoints thereafter

	AXS-05 (n=43)	Bupropion (n=37)	Difference	P-Value
<b>Primary Endpoint</b>				
Overall change in MADRS Total Score	-13.7	-8.8	-4.9	<0.001
<b>Secondary Endpoints</b>				
Change in MADRS Total Score at Week 1	-7.4	-4.5	-2.9	0.169
Change in MADRS Total Score at Week 2	-12.5	-7.8	-4.7	0.024
Change in MADRS Total Score at Week 6	-17.3	-12.1	-5.2	0.013

- At Week 1, AXS-05 was superior to bupropion on: CGI-I (18% vs. 3%;  $p=0.045$ ) and MADRS-6 response ( $\geq 50\%$  improvement; 16% vs. 3%;  $p=0.044$ )
- From Week 2, AXS-05 was superior to bupropion on: mean MADRS improvement (12.5 vs. 7.8;  $p=0.024$ ), MADRS remission ( $\leq 10$ ; 26% vs. 3%;  $p=0.004$ ), and CGI-S (1.41 vs. 0.9;  $p=0.049$ )

### Improvement in Symptoms of Depression with AXS-05 Compared to Placebo (GEMINI)



- AXS-05 achieved the primary endpoint ( $p=0.002$ )
- 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

	AXS-05 (n=156)	Placebo (n=162)	Difference	P-Value
<b>Primary Endpoint</b>				
Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
<b>Key Secondary Endpoints</b>				
Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007
Change in MADRS Total Score at Week 2	-11.1	-7.7	-3.4	<0.001

### Antidepressant Effects Across Multiple Outcomes (GEMINI)

	AXS-05	Placebo	Difference	P-Value
<b>Week One</b>				
Clinical Global Impression – Improvement % with marked/moderate improvement	22%	13%	9%	0.035
Clinical Global Impression – Severity Change from baseline	0.7	0.4	0.3	0.013
Patient Global Impression – Improvement % Reporting very much/much improved	14%	5%	9%	0.008
Clinical Response ( $\geq 50\%$ MADRS improvement)	15%	7%	8%	0.035
Quality of Life Improvement (Q-LES-Q-SF) Change from baseline in % of maximum possible score	9.1	5.8	3.3	0.031
<b>Week Two</b>				
Clinical Global Impression – Improvement % with marked/moderate improvement	44%	22%	22%	<0.001
Clinical Global Impression – Severity Change from baseline	1.1	0.7	0.4	<0.001
Patient Global Impression – Improvement % with marked/moderate improvement	30%	18%	12%	0.015
Clinical Remission (MADRS total score $\leq 10$ )	17%	8%	9%	0.013
Clinical Response ( $\geq 50\%$ MADRS improvement)	28%	17%	11%	0.020
Quality of Life Improvement (Q-LES-Q-SF) Change from baseline in % of maximum possible score	13.2	8.9	4.3	0.017
Improvement in Functioning (SDS Total Score) Change from baseline	6.8	4.5	2.3	0.003

### Safety and Tolerability

- AXS-05 was safe and well-tolerated in both trials
- In the two studies, the most commonly reported adverse events with AXS-05 were dizziness, nausea and headache
- Similar overall rates of adverse events were reported in the AXS-05 and bupropion treatment groups

## Conclusions

- AXS-05, a novel oral NMDA receptor antagonist, rapidly and statistically significantly improved depressive symptoms at Weeks 1 and 2 in placebo- and active- controlled trials**
- In both studies, remission from depressive symptoms was achieved by Week 2 and maintained over the 6 week treatment period**
- AXS-05 treatment resulted in statistically significant improvements in depression, quality of life and functioning as compared to placebo in the GEMINI trial**
- AXS-05 was statistically significantly superior to bupropion in improvement of depressive symptoms in the ASCEND trial**
- AXS-05 was generally safe and well tolerated in both studies. The most commonly reported adverse events were dizziness, nausea and headache**