Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder

Results From the GEMINI Phase 3, Double-Blind, Placebo-Controlled Trial

ASCP 2020 Oral Session

AXSOME THERAPEUTICS

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Major Depressive Disorder (MDD): Need for New, Innovative Treatments

- Major depressive disorder (MDD) is a disabling and life-threatening, biologically-based disorder as a leading cause of suicide[1,2]
- 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]
- Urgent need exists for new treatments with novel mechanisms of action, and faster onset of action, that are orally administered

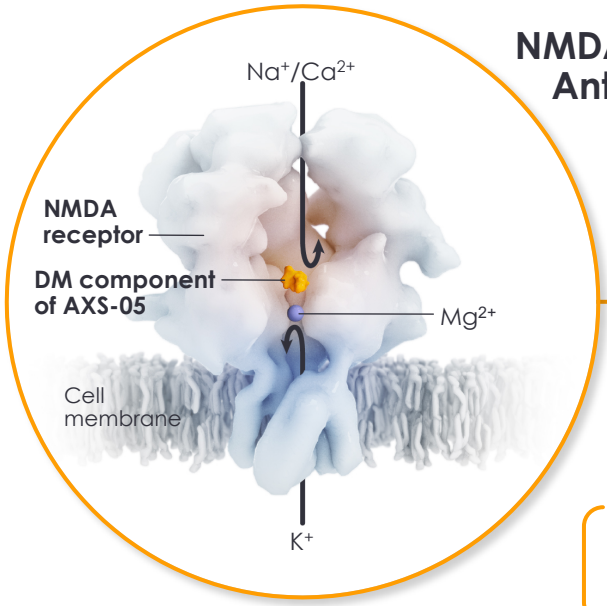
[1]Rush AJ, et al. *Am J Psychiatry.* 2006; 11(163):1905-1917.
[2]Kadriu B, et al. *Int J Neuropsychopharmacol.* 2019;22(2):119-135.
[3]Machado-Vieira R, et al. *Prog Neurobiol.* 2017;152:21-37.

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

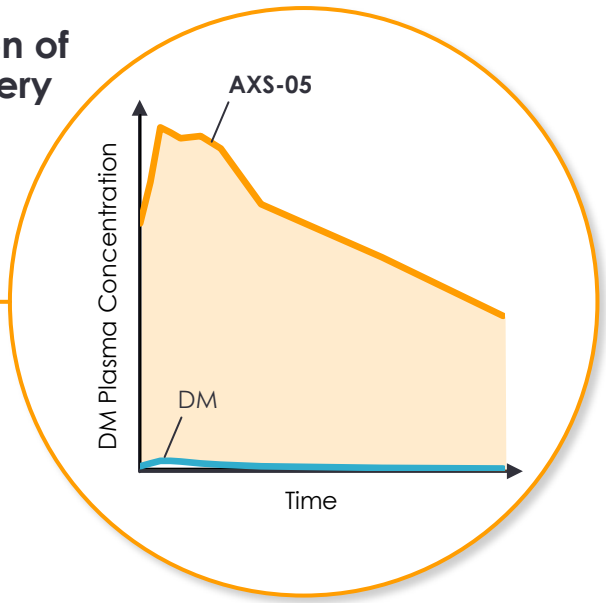


NMDA Receptor Antagonism

AXS-05

dextromethorphan/bupropion
modulated delivery tablet

Modulation of DM Delivery



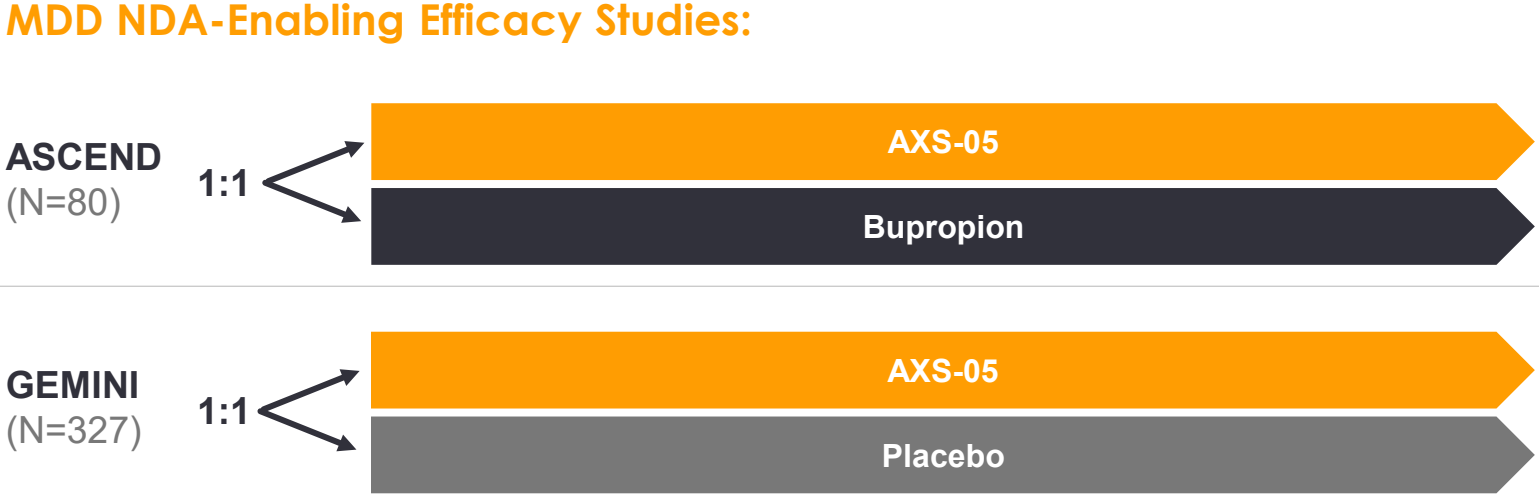
Sigma-1 Receptor Agonism

Monoamine Reuptake Inhibition

Abbreviations: DM = Dextromethorphan; Mg2+=magnesium ion; Na+=sodium ion; Ca+2=calcium ion; K+=potassium ion. Axsome data on file

AXS-05 Clinical Program in MDD

MDD NDA-Enabling Efficacy Studies:

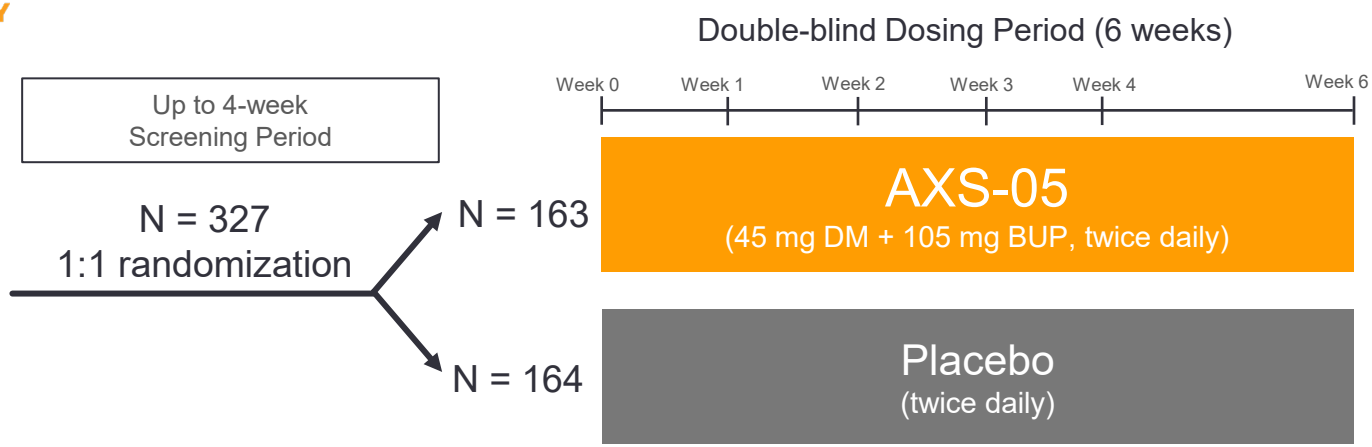


Open Label Safety Study:

GEMINI Trial of AXS-05 in MDD: Design Summary

GEMINI STUDY

A Phase 3 trial to assess the efficacy and safety of AXS-05 in the treatment of MDD



BUP = Bupropion; DM = Dextromethorphan

- **Primary Endpoint:**
  - Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6
- **Key Secondary Endpoints:**
  - MADRS change at Week 1 and Week 2; MADRS remission (≤10) at Week 6; MADRS response (≥50%) at Week 6
- **Secondary Endpoints:**
  - Clinical Global Impression of Improvement (CGI-I)
  - Clinical Global Impression of Severity (CGI-S)
  - Patient Global Impression of Improvement (PGI-I)
  - Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16)
  - Sheehan Disability Scale (SDS)
  - Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF)

GEMINI 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
- 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

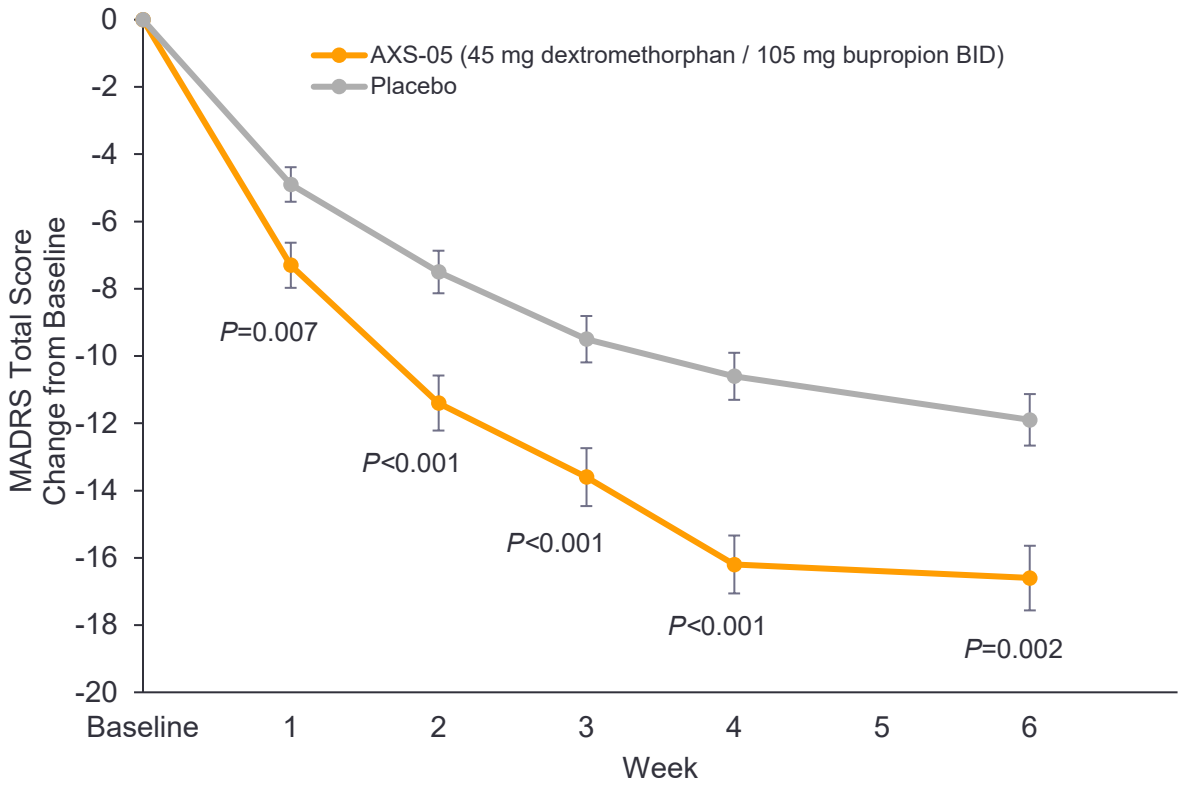
GEMINI Trial of AXS-05 in MDD: Demographics and Baseline Characteristics

	AXS-05 (45 mg DM / 105 mg BUP)	Placebo
Age (years)	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%)
Asian	9 (5.5%)	8 (4.9%)
Other or Not Reported	5 (3.1%)	9 (5.5%)
BMI (mg/kg^2)	29.2 (5.59)	29.4 (5.66)
MADRS Total Score	33.6 (4.43)	33.2 (4.36)
CGI-S Score	4.6 (0.59)	4.6 (0.57)

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

- Demographics and baseline characteristics were similar across both treatment groups
- Study completion rates were greater than 75% in both treatment groups

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



	AXS-05 (n=156)	Placebo (n=162)	Difference	*P*-Value
Primary Endpoint				
Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
Key Secondary Endpoint				
Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007

Notes: P-values calculated from LSMean. Abbreviations: BID = twice daily; MADRS = Montgomery-Åsberg Depression Rating Scale

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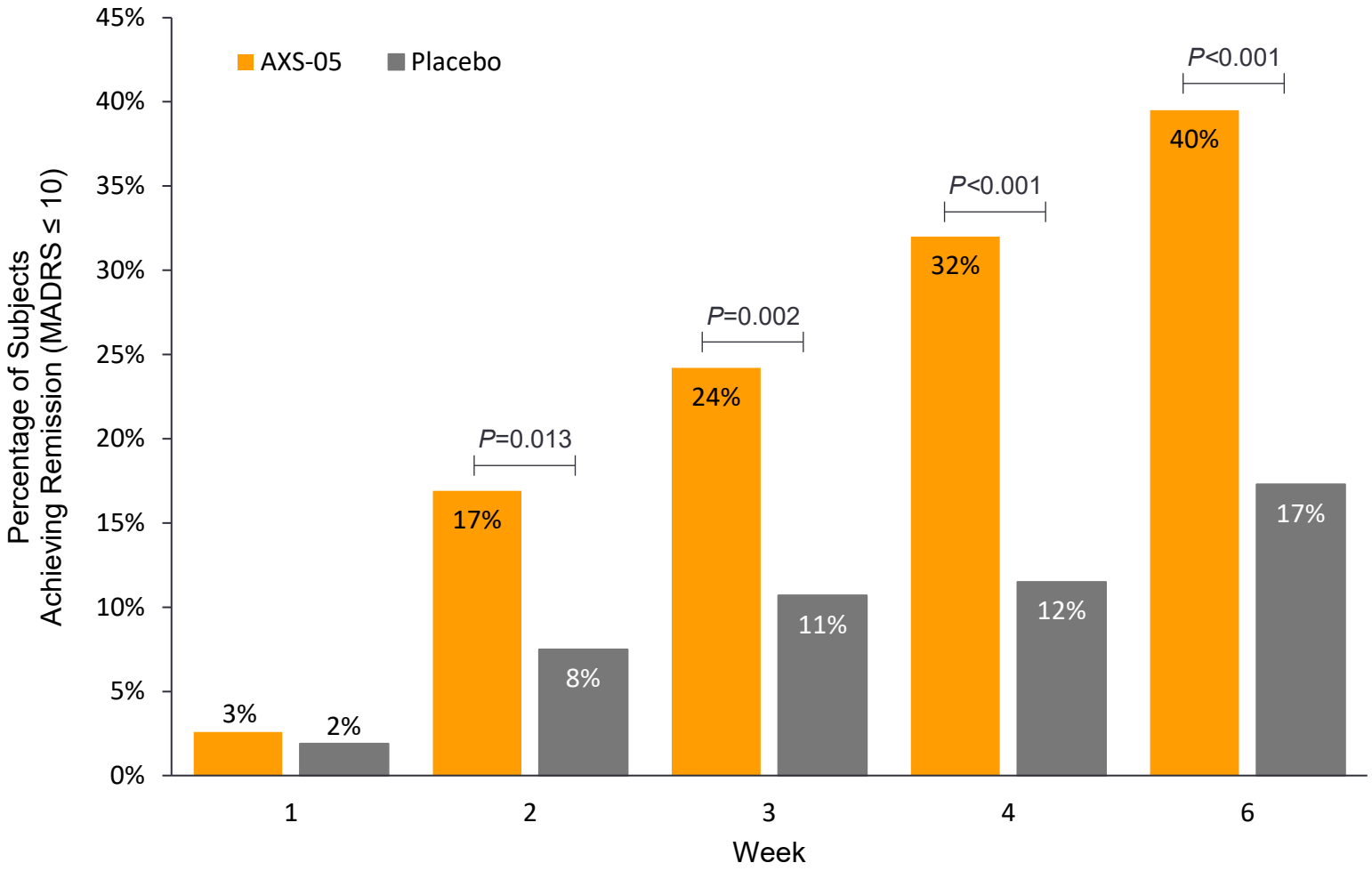
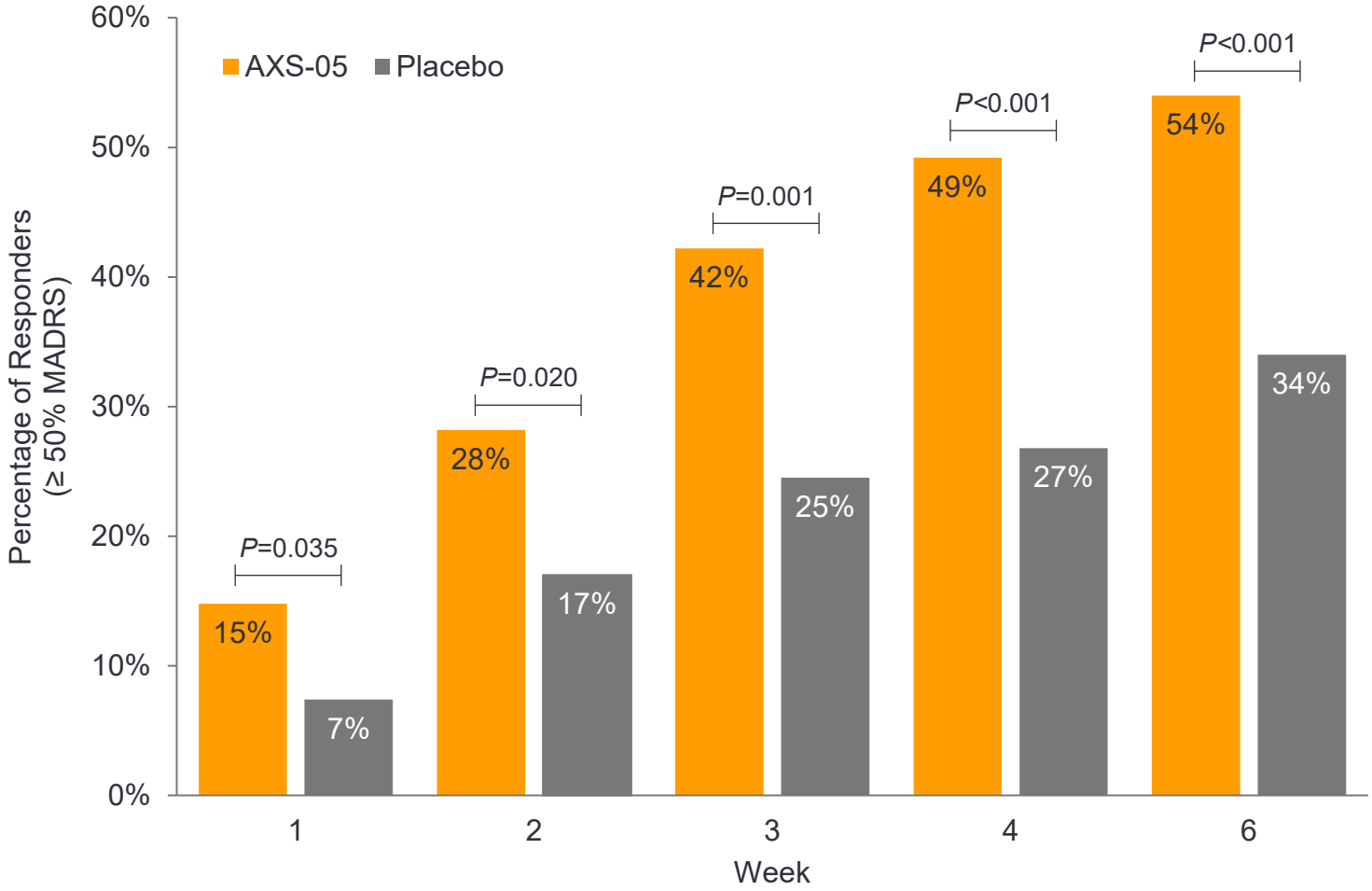
Rapid Achievement of Clinical Remission with AXS-05: MADRS ≤ 10



Early and Sustained Clinical Response with AXS-05: (≥ 50% MADRS improvement)



Rapid and Durable Improvements:
Global, Functional and Quality of Life Measures

	AXS-05 vs Placebo		
	Week 1	**Week 2**	**Week 6**
Depressive Symptom Improvement			
CGI-I *% with marked/moderate improvement*	22% vs 13% *p*=0.035	44% vs. 22% *p*=<0.001	58% vs. 43% *p*=0.016
CGI-S *Change from baseline*	0.7 vs. 0.4 *p*=0.013	1.1 vs 0.7 p=<0.001	1.7 vs. 1.2 p=0.002
PGI-I *% Reporting very much/much improved*	14% vs. 5% p=0.008	30% vs. 18% *p*=0.015	47% vs. 31% *p*=0.007
Quality of Life and Functional Improvement			
Q-LES-Q-SF *Change from baseline in % of maximum possible score*	9.1 vs 5.8 *p*=0.031	13.2 vs 8.9 *p*=0.017	19.8 vs. 14.4 *p*=0.011
Sheehan Disability Scale total score *Change from baseline*	4.6 vs. 3.4 ns	6.8 vs. 4.5 *p*=0.003	9.0 vs. 6.3 *p*=0.002

GEMINI Trial Results:
Safety & Tolerability

	AXS-05 (N = 162)	Placebo (N = 164)
Any Treatment-Emergent AE	**100 (61.7%)**	**74 (45.1%)**
Dizziness	26 (16.0%)	10 (6.1%)
Nausea	21 (13.0%)	14 (8.5%)
Headache	13 (8.0%)	6 (3.7%)
Diarrhea	11 (6.8%)	5 (3.0%)
Somnolence	11 (6.8%)	5 (3.0%)
Dry mouth	9 (5.6%)	4 (2.4%)

Adverse Events Occurring in ≥5% of Subjects. Data presented as number of subjects (% of subjects)

- Rates of discontinuation due to adverse events were low in both groups, 6.2% and 0.6%, for AXS-05 and placebo, respectively
- One serious adverse event in the AXS-05 arm, which was not related to study drug

GEMINI 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
- AXS-05 met the primary endpoint demonstrating statistically significant improvements on the MADRS total score versus placebo at Week 6
- Rapid antidepressant effects and clinically meaningful rates of response and remission seen as early as Week 1 and Week 2 and sustained to Week 6
- Substantial and statistically significant effects for AXS-05 as compared to placebo observed on multiple secondary endpoints
- Symptomatic benefits translated into statistically significant improvements on validated measurements of daily functioning and quality of life
- AXS-05 was safe and well tolerated in this trial and was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction

Q&A