**Introduction**

- Major depressive disorder (MDD) is a disabling, chronic and invariant condition. MDD is the leading cause of suicide in the U.S. 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 8-9 weeks). 1 All currently approved oral MDD agents work primarily through monoaminergic mechanisms. 2
- Clinical and preclinical evidence has implicated dysfunctional glutamatergic neurotransmission in the pathophysiology of MDD, suggesting a role for NMDA receptor antagonists in the treatment of MDD. 3
- NMDA receptor blockade may result in improved antidepressant response and faster onset of action.
- Activation of AMPA receptors induced by NMDA receptor blockade induces dendritic cascades mediated in neural plasticity that may underlie antidepressant effects. 1,4
- AXS-05 (desmethyl bupropion and bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. 2
- AXS-05 rapidly reduced depressive symptoms demonstrating numerical superiority to bupropion as early as Week 1, and statistically significant superiority at every timepoint thereafter including a 17.2 point reduction in the MADRS total score versus a 12.1 point reduction for bupropion (p=0.044).
- The novel mechanism of action of AXS-05 was associated with a differentiated clinical profile as compared to bupropion. 5
- AXS-05 was safe, well tolerated, and not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction. 5

**Methods**

- The ASCEND (Assessing Clinical Episodes in Depression) study was a Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial. 6
- Patients, 18-65 years of age inclusive, were required to meet the DSM-5 criteria for current MDD without psychotic features, and to have a MADRS score of ≥ 25 (described in Table 1) and CGI-S score of ≥ 4 at baseline.
- 80 patients with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were randomized to receive AXS-05 (45 mg desmethylbupropion plus 105 mg bupropion) (n=41), or bupropion (100 mg) (n=37), twice daily for 6 weeks. Prespecified efficacy analyses were conducted on an intention-to-treat basis.
- Patients without a confirmed diagnosis of moderate to severe MDD but who met all other study criteria (n=17) were randomized for assessment of safety to maintain the blinding of study investigators, as prespecified.
- Exclusion criteria included history of suicide attempts, organically-based symptoms, therapy, vago-vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the prior 6 months, schizophrenia, bipolar disorder, obsessive-compulsive disorder, psychotic symptoms secondary to any other general medical condition.
- The primary endpoint was the change from baseline in the MADRS total score, calculated at each time point in the study and averaged over the overall treatment effect.
- Secondary endpoints included: MADRS-6, Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), remission, safety and tolerability.
- Primary and secondary efficacy comparisons were based on the least squares mean difference between AXS-05 and bupropion treatment groups.

**Improvement in MADRS Total Score**

- AXS-05 achieved the primary endpoint demonstrating a statistically significant mean reduction from baseline in the MADRS total score, calculated at described timepoints in the study and averaged. of 13.7 points for AXS-05 compared to 8.8 for bupropion (p=0.004).
- The improvement over bupropion increased over time with statistical significance maintained at Week 6 (response rates of 63% for AXS-05 and 35% for bupropion, p=0.014).

**Early & Sustained Remission**

- Clinical remission, defined as a MADRS total score ≤ 12, was achieved by 47% of AXS-05 patients compared to 16% of bupropion patients (p=0.004).
- Remission rates were numerically greater for AXS-05 compared to bupropion as early as Week 1, and statistically significantly greater at Week 6 (28% vs. 9%, p=0.004) and at every timepoint thereafter.

**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.

**Conclusion**

- AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, representing a potential new mechanism 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 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 compared to currently approved agents for MDD.

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5. Bupropion is a registered trademark of GlaxoSmithKline. AXS-05 is an investigational NMDA receptor antagonist candidate in development by Axsome Therapeutics, Inc.