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

Amanda Jones1, Roger S. McIntyre1,2, Mark Jacobson3, Caroline Streicher3, Zach Thomas3, Herriot Tabuteau3

1University of Toronto, Toronto, CA; 2Brain and Cognition Discovery Foundation, Toronto, CA; 3Axsome Therapeutics, New York, NY.

Introduction

Major depressive disorder (MDD) is a serious disorder in which patients experience an inadequate response to current first-line treatments (SERT/SNRIs) and the majority of these inadecuately responders also fail to respond to subsequent treatments.1,2 Additional disease burden includes a high prevalence of comorbidity features of major depressive disorder (MDD) (39.3%) and an inability to feel.1-2 Inability to feel permeates a broad range of symptomatology in patients with MDD, including but not limited to decreased functioning and is a risk factor for non-suicidal self-injury.1-3

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.1,4-9

- The dextromethorphan component of AXS-05 is an antagonist of the MOR opioid receptor, an agonist at GABA-A receptors, and a sigma1 receptor, and a sigma2 receptor agonist.1,4-10
- The high affinity NMDA receptor antagonist component of AXS-05 is highly selective for the GluN1/GluN2B subunit, which is present in up to 75% of individuals diagnosed with MDD.1,11-13
- There is an urgent clinical need for:1-9

- AXS-05 rapidly and statistically significantly reduced MADRS total score at week 1, the first timepoint measured ($P<0.001$), at week 2, and at all timepoints thereafter.

Objective

- **GEMINI** was a phase 2, double-blind, placebo-controlled, multi-center, 1:1 trial, at which 327 adult patients with moderate to severe MDD were randomized to either AXS-05 or placebo (NCT04019704).
- A post-hoc analysis was conducted to determine the impact of AXS-05 as compared to placebo on the 5-item MADRS anhedonia subscale.
- **GEMINI** was designed to assess the efficacy of AXS-05 as compared to placebo in improving anhedonic symptoms in MDD as assessed by the MADRS anhedonia subscale.

Study Design: GEMINI

- **Primary Endpoint:** Change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 1.

- **Key Secondary Endpoints:** Change from baseline and at MADRS at Weeks 1 and 2

- **MADRS Anhedonia Subscale:** Change from baseline and rate of response as measured by the MADRS anhedonia subscale, which includes items:
  - Sexual desire
  - Reported sadness
  - Concentration difficulties
  - Lassitude
  - Inability to feel

Results

- **Change from baseline on the 5-item MADRS anhedonia subscale is highly statistically significant** ($P<0.001$).

- **Previous research has demonstrated that the MADRS anhedonia subscale is highly predictive of clinical response, and an important indicator of anhedonia present in MDD.**

- AXS-05 rapidly and statistically significantly reduced MADRS total score at week 1, the first timepoint measured ($P<0.001$), at week 2, and at all timepoints thereafter.

Demographics and Baseline Characteristics

- AXS-05 patients versus 36% of placebo patients at 4.9% for AXS-05 compared to placebo at Week 1 ($p<0.001$) and at every timepoint thereafter.

- **Disclosures:**

- **Safety and Tolerability:**

- **Conclusions:**

- AXS-05 was well tolerated.
- These data support the efficacy of AXS-05 in a broad range of symptomatology in patients with MDD.

References

9. Business Wire. 2019. "Axsome Therapeutics, Inc Announces Positive Full-Data Set Results from Phase 2, Double-Blind, Randomized, Placebo-Controlled Study of AXS-05 in Major Depressive Disorder (MDD)" (NCT04019704)."