Axsome Therapeutics Announces Publication of Pivotal ASCEND Phase 2 Trial of AXS-05 in Major Depressive Disorder in The American Journal of Psychiatry

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In this study, AXS-05 (dextromethorphan-bupropion) demonstrated rapid, substantial, and statistically significant antidepressant efficacy compared with the active comparator bupropion

NEW YORK, May 18, 2022 /PRNewswire/ -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company developing and delivering novel therapies for the management of central nervous system (CNS) disorders, today announced the publication of the results from the pivotal ASCEND Phase 2 clinical trial of AXS-05 (dextromethorphan-bupropion) in major depressive disorder (MDD). AXS-05 is a novel, oral, investigational N-methyl-D-aspartate (NMDA) receptor antagonist with multimodal activity. The article, "Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized, Double-Blind, Controlled Trial," was published today in *The American Journal of Psychiatry* and is available in full here.

"Major depressive disorder is highly prevalent, debilitating and potentially life-threatening. There is an urgent need for mechanistically new treatments that are effective and well tolerated," said Dan Iosifescu, MD, Professor of Psychiatry at the New York University School of Medicine, Director of the Clinical Research Division at the Nathan Kline Institute for Psychiatric Research, and co-author of the publication. "Due to its novel mechanism of action targeting glutamate and sigma-1 receptors, and to its robust antidepressant efficacy demonstrated in this study, AXS-05 has the potential to become an important and very useful new treatment for patients with major depressive disorder."

"We are very pleased with the publication of the ASCEND trial results in *The American Journal of Psychiatry*, the most widely read psychiatric journal in the world[1]," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "ASCEND is one of the pivotal efficacy trials that forms the basis of our NDA for AXS-05 in depression, which is currently under review by the FDA. Axsome is positioned to move expeditiously to make this product available to patients as quickly as possible, should it be approved."

The ASCEND trial assessed the efficacy and safety of AXS-05 versus the active comparator bupropion in patients with MDD. A total of 80 patients with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were randomized to receive AXS-05 (45 mg dextromethorphan/105 mg bupropion tablet) (n=43), or bupropion (105 mg tablet) (n=37), once daily for the first 3 days and twice daily thereafter, for a total of 6 weeks. The primary endpoint was overall treatment effect on the Montgomery-Åsberg Depression Rating Scale (MADRS) score (average of the change from baseline for weeks 1–6).

In the trial, AXS-05 demonstrated rapid, substantial, and statistically significant improvement in depressive symptoms and induction of remission compared with bupropion. The mean change from baseline in MADRS score over weeks 1–6 was significantly greater with AXS-05 than with bupropion (-13.7 points vs. -8.8 points; least-squares mean difference=-4.9; p<0.001). The MADRS score change with AXS-05 was significantly greater than with bupropion at week 2 and every time point thereafter (week 6: -17.3 vs. -12.1 points; least-squares mean difference=-5.2; p=0.013). Remission rates were significantly greater with AXS-05 at week 2 and every time point thereafter (week 6: 46.5% vs. 16.2%; least-squares mean difference=30.3%; p=0.004). Most secondary outcomes favored AXS-05.

AXS-05 was generally well tolerated in the trial. The most common adverse events with AXS-05 were dizziness, nausea, dry mouth, decreased appetite, and anxiety. AXS-05 was not associated with psychotomimetic effects, weight gain, or sexual dysfunction.

The article was published today online in *The American Journal of Psychiatry* in advance of the corresponding upcoming print issue.

About AXS-05

AXS-05 (dextromethorphan-bupropion) is a novel, oral, patent protected, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of major depressive disorder and other central nervous system (CNS) disorders. AXS-05 utilizes a proprietary formulation and dose of dextromethorphan and bupropion, and Axsome's metabolic inhibition technology, to modulate the delivery of the components. The dextromethorphan component of AXS-05 is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, which is a novel mechanism of action, meaning it works differently than currently approved oral therapies for major depressive disorder. The dextromethorphan component of AXS-05 is also a sigma-1 receptor agonist. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor. AXS-05 is currently covered by more than 100 issued U.S. and international patents, with expiration dates out to 2040. AXS-05 has been granted FDA Breakthrough Therapy designations for the treatment of MDD and for the treatment of Alzheimer's disease agitation. A new drug application (NDA) for AXS-05 for the treatment of major depressive disorder is under review by the FDA. AXS-05 is not approved by the FDA.

About Axsome Therapeutics, Inc.

Axsome Therapeutics, Inc. is a biopharmaceutical company developing and delivering novel therapies for CNS conditions that have limited treatment options. Through development of therapeutic options with novel mechanisms of action, we are transforming the approach to treating CNS conditions.

At Axsome, we are committed to developing products that meaningfully improve the lives of patients and provide new therapeutic options for physicians. For more information, please visit the Company's website at axsome.com. The Company may occasionally disseminate material, nonpublic information on the company website.

Forward Looking Statements

Certain matters discussed in this press release are "forward-looking statements". We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company's statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the continued commercial success of our newly acquired Sunosi product; the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials, and the number or type of studies or nature of results necessary to support the filing of an NDA for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain FDA or other regulatory authority approval of, or other action with respect to, our product candidates (including, but not limited to, whether potential filing issues or issues identified by FDA during the substantive review may impact the potential approvability of the Company's NDA submission for AXS-05 in MDD or the timing of such approval; whether issues identified by FDA in the complete response letter may impact the potential approvability of the Company's NDA for AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment for the MOMENTUM clinical trial; the potential for the ASCEND clinical trial, combined with the GEMINI clinical trial results, to provide a basis for approval of AXS-05 for the treatment of major depressive disorder and accelerate its development timeline and commercial path to patients; the Company's ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the success of the Company's license agreements; the acceptance by the market of the Company's product candidates, if approved; the Company's anticipated capital requirements, including the amount of capital required for the continued commercialization of Sunosi and for the Company's commercial launch of its product candidates, and the potential impact on the Company's anticipated cash runway; unforeseen circumstances or other disruptions to normal business operations arising from or related to COVID-19; and other factors, including general economic conditions and regulatory developments, not within the Company's control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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1. American Psychiatric Association. About The American Journal of Psychiatry. *Psychiatry Online*. 2022. https://ajp.psychiatryonline.org/about

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