Axsome Therapeutics Announces Late-Breaking Presentations of Positive Results of the EVOLVE Trial of AXS-05 in Major Depressive Disorder After Prior Treatment Failures at the American Society of Clinical Psychopharmacology (ASCP) 2022 Annual Meeting

June 1, 2022

Rapid, substantial, and durable improvement in depressive symptoms (MADRS), and functioning (SDS) with AXS-05, sustained over 12 months, (p<0.001 for all vs. baseline)

Rapid, substantial, and durable reductions in anxiety (HAM-A) with AXS-05, sustained over 12 months, (p<0.001 vs. baseline)

NEW YORK, June 01, 2022 (GLOBE NEWSWIRE) -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company developing and delivering novel therapies for the management of central nervous system (CNS) disorders, today announced positive results from the long-term, open-label EVOLVE trial of AXS-05 (dextromethorphan-bupropion) in major depressive disorder (MDD). EVOLVE assessed the long-term efficacy and safety of AXS-05 in patients failing one or more prior antidepressants during the current major depressive episode. Patients treated with AXS-05 experienced rapid, substantial, and durable improvements in depressive symptoms, anxiety, and functioning, that were sustained over 12 months. These new data were accepted as late-breaking presentations, and are being presented today at the American Society of Clinical Psychopharmacology (ASCP) 2022 Annual Meeting, being held in Scottsdale, Arizona and virtually.

EVOLVE (Evaluation of NMDA Modulation for Depressive Episodes) was an open-label, U.S. trial in which patients with MDD who had failed at least one prior antidepressant were treated with AXS-05 (45 mg dextromethorphan/105 mg bupropion tablet) twice daily for up to 15 months. The objective of the trial was to assess the effect of AXS-05 on depression, anxiety, and functioning in patients with MDD who had failed prior treatment, as well as safety. Eligible patients were directly enrolled into the study, or had rolled in following completion of a prior AXS-05 study (MERIT). A total of 186 patients were enrolled, consisting of 146 directly enrolled and 35 roll-over patients. Results for the directly enrolled patients were analyzed. The primary endpoint was the change from baseline to week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. The change in anxiety symptoms was assessed using the Hamilton Anxiety Rating Scale (HAM-A). Functioning was assessed using the Sheehan Disability Scale (SDS). Statistical analysis was performed comparing the measures at each timepoint to baseline values as pre-specified (significance level of 0.05, two-sided).

In the trial, AXS-05 rapidly, durably, and substantially improved depressive symptoms, induced remission of depression, and improved functioning in patients with at least one prior antidepressant treatment failure. The mean MADRS total score at baseline was 32.2. Mean improvements from baseline to weeks 1, 2, and 6 in MADRS total scores were -9.1 points, -13.3 points, and -20.4 points, respectively ($p<0.001$ for all). Improvements on the MADRS were durable through month 9 (-23.3 points, $p<0.001$) and month 12 (-24.5 points, $p<0.001$). Remission of depression (MADRS ≤10) was achieved by 16%, 32%, and 46% of patients at weeks 2, 4, and 6, respectively. Remission of depression was durable, with 65% of patients remitting at month 6 and 68% at month 12. Substantial improvements on the SDS were seen at all timepoints from a baseline value of 17.5 ($p<0.001$ for all). Functional remission (SDS ≤6) was achieved by 18%, 31%, and 40% and of patients at week 1, 2, and 6, respectively. Functional remission was durable, being achieved by 54% of patients at month 6 and 59% at month 12.

AXS-05 also rapidly, durably, and substantially reduced anxiety, and induced remission of anxiety in a substantial proportion of patients with MDD. The mean HAM-A score at baseline was 15.6. Mean improvements from baseline to weeks 1, 2, and 6 in HAM-A scores were -3.4 points, -5.5 points, and -8.6 points, respectively ($p<0.001$ for all). Improvements on the HAM-A were durable through month 6 (-10.2 points, $p<0.001$) and month 12 (-10.2 points, $p<0.001$). Remission of anxiety (HAM-A ≤ 7) was achieved by 36%, 51%, and 58% of patients at weeks 2, 4, and 6, respectively. Remission of anxiety was durable, with 75% of patients remitting at month 6 and 78% at month 12.

AXS-05 was generally well tolerated with long-term treatment and exhibited a safety profile consistent with that observed in previously reported trials.

"We are pleased to announce the results of the EVOLVE trial as late-breaking presentations at this year's ASCP annual meeting, which further elucidate the differentiated clinical profile of AXS-05 in depression" said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "These results add to the significant and growing body of clinical data showing rapid, substantial, and durable effects of AXS-05 on a broad range of symptoms in patients with depression. The improvement of anxiety symptoms observed with AXS-05 are notable as anxiety occurs in nearly half of individuals with depression and is associated with depression that is more difficult to treat."

Details of the poster presentations are as follows:

Title: AXS-05 (Dextromethorphan-Bupropion) Improves Depressive Symptoms and Functioning in Patients with One Prior Treatment Failure: Results from the EVOLVE Long-Term, Open-Label Study
Presentation Number: W56
Session: Poster Session I
Date: Wednesday, June 1, 2022
Time: 11:15 PM – 1 PM MST

Location: Palomino Ballroom 4-10, Fairmont Scottsdale Princess, Scottsdale, AZ

Title: Improvement in Anxiety Symptoms in Depressed Patients Treated with AXS-05 (Dextromethorphan-Bupropion): Results from the EVOLVE Open-label, Long-term Study
Presentation Number: W57
Session: Poster Session I
Date: Wednesday, June 1, 2022
Time: 11:15 PM – 1 PM MST
Location: Palomino Ballroom 4-10, Fairmont Scottsdale Princess, Scottsdale, AZ

About AXS-05

AXS-05 (dextromethorphan-bupropion) is a novel, oral, patent protected, investigational N-methyl-D-aspartate (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 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 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 a new drug application ("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 U.S. Food and Drug Administration ("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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