Axsome Therapeutics Announces AXS-05 Achieves Primary Endpoint in the ACCORD Phase 3 Trial in Alzheimer's Disease Agitation

November 28, 2022

AXS-05 statistically significantly delayed time to relapse of Alzheimer's disease agitation versus placebo (p=0.014, primary endpoint)

AXS-05 statistically significantly prevented relapse of Alzheimer's disease agitation versus placebo (p=0.018, key secondary endpoint)

Statistically significant improvement in Alzheimer's disease agitation, as measured by the CMAI total score, starting at Week 1 with open-label AXS-05 (p<0.001 vs baseline, all timepoints)

Improvement in Alzheimer's disease agitation, assessed by the modified Alzheimer's Disease Cooperative Study-CGIC scale, achieved by 66% of patients at 2 weeks and 86% at 5 weeks

Improvement in Alzheimer's disease agitation, assessed by the PGI-C scale, achieved by 68% of patients at 2 weeks and 89% at 5 weeks

No treatments are currently approved for Alzheimer's disease agitation

NEW YORK, Nov. 28, 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 that AXS-05, a novel, oral, investigational NMDA receptor antagonist with multimodal activity, met the primary and key secondary endpoints in the ACCORD (Assessing Clinical Outcomes in Alzheimer's Disease Agitation) Phase 3 trial, by substantially and statistically significantly delaying the time to relapse and preventing relapse of agitation in patients with Alzheimer's disease, as compared to placebo. The ACCORD study was a double-blind, placebo-controlled, multi-center, randomized withdrawal, U.S. trial which treated 178 patients with Alzheimer's disease agitation. Patients achieving a sustained clinical response after open-label treatment with AXS-05 were randomized (n=108) in a 1:1 ratio to continue treatment with AXS-05 or to discontinue AXS-05 and switch to placebo. AXS-05 has been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's disease agitation. There are currently no FDA-approved treatments for Alzheimer's disease agitation.

AXS-05 met the primary endpoint by substantially and statistically significantly delaying the time to relapse of agitation symptoms as compared to placebo, with a hazard ratio for time to relapse of 0.275 (p=0.014), representing a 3.6-fold lower risk of relapse compared to placebo. AXS-05 also met the key secondary endpoint of relapse prevention, based on the rates of relapse during the double-blind treatment period (7.5% of AXS-05 patients vs. 25.9% of placebo patients, p=0.018). Relapse was defined as a ≥10-point worsening in the CMAI total score from randomization or a CMAI total score greater than that at study entry; or hospitalization or other institutionalization due to agitation associated with Alzheimer's disease.

With open-label treatment with AXS-05, patients experienced rapid, substantial, and statistically significant improvement compared to baseline in agitation symptoms. Statistically significant improvement on the Cohen Mansfield Agitation Inventory (CMAI) was seen with open-label AXS-05 treatment at all timepoints starting at Week 1 (p<0.001), with mean reductions from baseline of 11.0 points at Week 2 (p<0.001), and 20.6 points at Week 5 (p<0.001). Improvements were also significant with open-label AXS-05 treatment on all CMAI subscales including the Physically Aggressive subscale at all timepoints (p<0.001).

Jeffrey Cummings, MD, ScD, Director Emeritus of the Cleveland Clinic Lou Ruvo Center for Brain Health, and Chambers Professor of Brain Science at the University of Nevada Las Vegas said, "Agitation is one of the most troubling and consequential aspects of Alzheimer's disease for patients and their caregivers as it is associated with early nursing home placement, accelerated cognitive decline, and increased mortality. The results of the ACCORD trial demonstrate convincing clinical activity for AXS-05 on agitation associated with Alzheimer's disease based on both a significant delay in symptom relapse as well as a reduction of relapse compared to placebo. Treatment with AXS-05 during the open-label period in a large cohort of patients resulted in rapid and clinically meaningful improvements in Alzheimer's disease agitation. The improvements were especially notable since they were seen on the aggressive symptom subscales of the agitation measures. Agitation occurs in the majority of patients with Alzheimer's disease and there are currently no treatments approved for this condition. AXS-05 could potentially fill this high unmet medical need for patients and their caregivers, if approved, based on the observed positive efficacy and favorable safety and tolerability results."

Rapid and substantial improvement in Alzheimer's disease agitation was reported by both clinicians and caregivers on global measures. Clinicians reported improvement in agitation in 66.3% of patients at Week 2 and 86.3% at Week 5 after treatment with AXS-05, as assessed using the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC). Caregivers reported improvement in agitation in 67.5% of patients at Week 2 and 89.3% at Week 5 after treatment with AXS-05, as assessed using the Patient Global Impression of Change (PGI-C) rated by the caregiver.

Caregiver distress and burden, patient quality of life, and depressive symptoms were all statistically significantly improved compared to baseline after patients were treated with open-label AXS-05. Caregiver distress was assessed using the NPI Agitation and Aggression Caregiver Distress score (p<0.001, at Weeks 4 and 8). Caregiver burden was assessed using the Zarit Burden Interview (ZBI) (p=0.006 at Week 4, p=0.003 at Week 8). Patient quality of life was assessed using the caregiver rated Quality of Life Alzheimer's Disease (QoL-AD) scale (p<0.001 at Week 4, p=0.013 at Week 8).

Depressive symptoms were assessed using the Cornell Scale for Depression in Dementia (CSDD) ($p<0.001$, at Weeks 4 and 8).

Herriot Tabuteau, MD, Chief Executive Officer of Axsome said, “With the positive results from ACCORD, AXS-05 has now demonstrated efficacy in the treatment of Alzheimer’s disease agitation in two well-controlled trials. In addition to the strong results versus placebo in the double-blind period, results from the open-label period evidenced rapid, substantial, and significant improvements in Alzheimer’s disease agitation versus baseline with AXS-05 treatment. The ACCORD results complement, and are consistent with, those from the previously completed positive ADVANCE-1 trial. We intend to discuss these findings with the FDA in the context of the ongoing clinical development of AXS-05 in this indication, with the goal of providing a much needed treatment to the millions of patients living with Alzheimer’s disease agitation and their caregivers.”

The rates of adverse events observed in the double-blind period were 28.3% in the AXS-05 group and 22.2% in the placebo group. Discontinuations in the double-blind period due to adverse events were low (0% for AXS-05 and 1.9% for placebo). One serious adverse event was reported in the AXS-05 group (faecaloma), which was determined by the investigator to be not related to study medication, and 2 serious adverse events were reported in the placebo group (cardiac arrest, femur fracture). Falls were reported in 4 patients in the AXS-05 group, none of which were associated with serious adverse events and all of which were determined by the investigators to be not related to study medication, and in 2 patients in the placebo group, one of which was associated with a femur fracture. One death was reported in the placebo group. There was no evidence of cognitive decline for patients treated with AXS-05 as shown by the Mini-Mental State Examination (MMSE), a widely utilized measure of general cognitive function. Treatment with AXS-05 was not associated with sedation.

AXS-05 was granted Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation by the FDA in June 2020. The FDA Breakthrough Therapy designation was supported by the positive results of the ADVANCE-1 trial. A Breakthrough Therapy designation is granted to potentially expedite development and review timelines for a promising investigational medicine when preliminary clinical evidence indicates it may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies for a serious or life-threatening condition.

Open-label Period Results Summary

A total of 178 patients were treated with open-label AXS-05 for up to 9 weeks and assessed for efficacy. The primary timepoint for open-label efficacy assessments was 5 weeks, and the key secondary timepoint was 2 weeks. P-values were calculated versus baseline.

- The mean CMAI total score was 70.9 at baseline.
- Treatment with AXS-05 was associated with a mean reduction from baseline in the CMAI total score of 6.7 points at Week 1, 11.0 points at Week 2, and 20.6 points at Week 5 ($p<0.001$ for all).
- Clinical response on the CMAI (defined as ≥30% reduction from baseline) after treatment with AXS-05 was achieved by 21.8% of patients at Week 1, 40.4% of patients at Week 2, and 70.0% of patients at Week 5.
- Treatment with AXS-05 was also associated with improvements on all CMAI subscales including the Physically Aggressive subscale at all timepoints ($p<0.001$).
- Improvement in Alzheimer’s disease agitation, assessed using the clinician rated mADCS-CGIC, was achieved by 47.1% of patients at Week 1, 66.3% of patients at Week 2, and 86.3% of patients at Week 5, after treatment with AXS-05.
- Improvement in Alzheimer’s disease agitation, assessed using the caregiver rated PGI-C, was achieved by 51.2% of patients at Week 1, 67.5% of patients at Week 2, and 89.3% of patients at Week 5, after treatment with AXS-05.
- Caregiver distress, assessed using the NPI Agitation and Aggression Caregiver Distress score, was significantly reduced after treatment with AXS-05 ($p<0.001$, at Weeks 4 and 8).
- Caregiver burden, assessed using the ZBI, was significantly reduced after treatment with AXS-05 ($p=0.006$ at Week 4, $p=0.003$ at Week 8).
- Patient quality of life, assessed using the caregiver rated QoL-AD scale, was significantly improved after treatment with AXS-05 ($p<0.001$ at Week 4, $p=0.013$ at Week 8).
- Depressive symptoms, assessed using the CSDD, were significantly reduced after treatment with AXS-05 ($p<0.001$, at Weeks 4 and 8).

Double-blind Period Results Summary

A total of 108 patients were randomized, 53 to continued treatment with AXS-05, and 55 switched to placebo. The mean CMAI total scores at randomization were 43.7 and 44.9 for the AXS-05 and placebo groups respectively.

- AXS-05 met the primary endpoint by substantially and statistically significantly delaying the time to relapse of Alzheimer’s disease agitation as compared to placebo (hazard ratio for time to relapse of 0.275, $p=0.014$), demonstrating a 3.6-fold lower risk of relapse compared to placebo.
- AXS-05 met the key secondary endpoint by preventing relapse of Alzheimer’s disease agitation as compared to placebo, with 7.5% of AXS-05 patients relapsing versus 25.9% of patients switched to placebo ($p=0.018$).

- The rates of adverse events in the double-blind period were 28.3% in the AXS-05 group and 22.2% in the placebo group. Discontinuations in the double-blind period due to adverse events were low (0% for AXS-05 and 1.9% for placebo).

About the ACCORD Study

ACCORD (Assessing Clinical Outcomes in Alzheimer's Disease Agitation) was a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial to evaluate efficacy and safety of AXS-05 in patients with Alzheimer's disease (AD) agitation. Patients with a diagnosis of probable Alzheimer's disease and clinically meaningful agitation associated with their disease were enrolled into a 9-week, open-label period, during which they were treated with AXS-05 and monitored for a sustained clinical response. Sustained clinical response was defined as a ≥30% improvement from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) total score and improvement on the PGI-C (score of ≤3) that are both maintained for at least 4 consecutive weeks.

Patients who experienced a sustained clinical response during the open-label treatment period were then randomized in a 1:1 ratio, to continue treatment with AXS-05 or to switch to placebo treatment, in a double-blind fashion for up to 26 weeks. Treatment was continued until either a relapse of agitation symptoms or the end of the 26-week double-blind period, whichever occurred first. Relapse was defined as a ≥10-point worsening in the CMAI total score from randomization or a CMAI total score greater than that at study entry; or hospitalization or other institutionalization due to agitation associated with Alzheimer's disease.

A total of 178 patients were enrolled into the open-label period and treated with AXS-05, and 108 patients were randomized to continue on AXS-05 (n=53) or to switch to placebo (n=55). The mean Cohen-Mansfield Agitation Inventory (CMAI) total score at baseline study entry was 70.9. The mean CMAI total scores at randomization were 43.7 (AXS-05) and 44.9 (placebo). The minimum score on the CMAI is 29, corresponding to the total absence of symptoms, with higher scores corresponding to greater agitation. The primary endpoint in the study was time from randomization to relapse of Alzheimer's disease agitation calculated by the Kaplan-Meier estimates and the hazard ratio. The key secondary endpoint, to assess relapse prevention, was the percentage of patients who relapsed. The primary timepoint for open-label efficacy assessments was Week 5 and the key secondary timepoint was Week 2. P-values for the open-label period were calculated versus baseline.

About Alzheimer's Disease (AD) Agitation

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, and behavioral and psychological symptoms including agitation. AD is the most common form of dementia and afflicts an estimated 6 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050.[4] Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition.[1] Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality.[1-3] There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

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 Alzheimer's disease (AD) agitation 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, and 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 covered by a robust patent estate extending out at least to 2037-2040. AXS-05 was granted FDA Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation in June 2020. AXS-05 is not approved by the FDA for the treatment of AD agitation.

About Axsome Therapeutics, Inc.

Axsome Therapeutics, Inc. is a biopharmaceutical company developing and delivering novel therapies for central nervous system (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 Sunosi and Auvelity products and the success of our efforts to obtain any additional indication(s) with respect to soriamfetol and/or AXS-05; 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; 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 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 products and product candidates, if approved; the Company's anticipated capital requirements, including the amount of capital required for the

continued commercialization of Sunosi and Auvelity and for the Company's commercial launch of its other 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.

Axsome Contact:
Mark Jacobson
Chief Operating Officer
Axsome Therapeutics, Inc.
22 Cortlandt Street, 16th Floor
New York, NY 10007
Tel: 212-332-3243
Email: mjacobson@axsome.com
www.axsome.com

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Source: Axsome Therapeutics, Inc.