Axsome Therapeutics Announces AXS-05 Achieves Primary Endpoint in the ADVANCE-1 Pivotal Phase 2/3 Trial in Alzheimer's Disease Agitation

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Statistically significant improvement in Alzheimer's disease agitation, as measured by the CMAI total score compared to placebo (p=0.010, primary endpoint)

Demonstrated rapid and substantial improvement in Alzheimer's disease agitation starting at week 2 with statistical significance at week 3 compared to placebo (p=0.007)

Statistically significant rates of clinical response (p=0.005) on the CMAI and improvement on the modified Alzheimer's Disease Cooperative Study-CGIC scale for agitation (p=0.036) compared to placebo

Well-tolerated and not associated with cognitive impairment or sedation

No treatments are currently approved for Alzheimer's disease agitation

Company to host conference call today at 8:00 AM ET

NEW YORK, April 27, 2020 (GLOBE NEWSWIRE) -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a clinical-stage biopharmaceutical company developing 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 endpoint in the ADVANCE-1 Phase 2/3 trial and rapidly, substantially, and significantly improved agitation in patients with Alzheimer's disease as compared to placebo. The ADVANCE-1 (Addressing Dementia via Agitation-Centered Evaluation) study was a randomized, double-blind, controlled, multicenter, U.S. trial, in which 366 Alzheimer's disease patients were randomized to treatment with AXS-05 (dextromethorphan/bupropion modulated delivery tablet, dose escalated to 45 mg/105 mg twice daily), bupropion (dose escalated to 105 mg twice daily), or matching placebo, for 5 weeks.

There are currently no FDA-approved treatments for Alzheimer's disease agitation. Alzheimer's disease is the most common form of dementia and is characterized by cognitive decline, and behavioral and psychological symptoms including agitation. Agitation is observed in up to 70% of patients with Alzheimer's disease and is associated with accelerated cognitive decline, earlier nursing home placement, and increased mortality risk [1-3]. AXS-05 has been granted FDA Fast Track designation for the treatment of Alzheimer's disease agitation.

AXS-05 met the primary endpoint by demonstrating a statistically significant mean reduction in the Cohen Mansfield Agitation Inventory (CMAI) total score compared to placebo at Week 5, with mean reductions from baseline of 15.4 points for AXS-05 and 11.5 points for placebo (p=0.010). These results represent a mean percentage reduction from baseline of 48% for AXS-05 versus 38% for placebo. The CMAI is a 29-item caregiver-rated scale that assesses the frequency of agitation-related behaviors in patients with dementia, including excessive motor activity such as pacing and restlessness, verbal aggression such as screaming and shouting, and physical aggression such as grabbing, pushing, and hitting. AXS-05 was also superior to bupropion on the CMAI total score (p<0.001), establishing component contribution.

AXS-05 rapidly improved agitation symptoms. Improvement on the CMAI total score with AXS-05 was numerically superior to placebo starting at Week 2, achieving statistical significance at Week 3 (p=0.007) only one week after full dosing with AXS-05.

A statistically significantly greater proportion of patients achieved a clinical response on the CMAI, defined as a 30% or greater improvement from baseline, with AXS-05 as compared to placebo (73% versus 57%, p=0.005). These results were consistent with clinicians' global assessments of change measured using the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC). AXS-05 demonstrated statistically significantly greater improvement in agitation as compared to placebo on this measure (p=0.036).

"I am very pleased to see the promising results of the ADVANCE-1 trial, providing clear evidence of reduced agitation in Alzheimer's disease by this investigational medicine," said Jeffrey Cummings, M.D., Sc.D., 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. "The clinically significant reductions in agitation were accompanied by a favorable safety and tolerability profile. Agitation occurs in the majority of patients with Alzheimer's disease, is very distressing to patients and their families, and is associated with greater risk of institutionalization and accelerated progression to severe dementia and death. Given the lack of approved treatments for Alzheimer's disease agitation, and the safety concerns and modest or uncertain efficacy of currently used off-label treatments, the AXS-05 study results represent a meaningful step forward toward urgently needed treatment for this serious complication of Alzheimer's disease."

AXS-05 was well tolerated in the trial. The most commonly reported adverse events in the AXS-05 arm were somnolence (8.2% for AXS-05 versus 4.1% for bupropion and 3.2% for placebo), dizziness (6.3%, 10.2%, 3.2%, respectively), and diarrhea (4.4%, 6.1%, 4.4%, respectively). The rates of discontinuation due to adverse events were 1.3%, 2.0%, and 1.3% in the AXS-05, bupropion, and placebo arms, respectively. Serious adverse events were reported in 3.1% of patients treated with AXS-05, compared to 8.2% of bupropion- and 5.7% of placebo-treated patients. No serious adverse events were deemed to be related to study drug in any treatment arm. There was one death in the placebo arm, one in the bupropion arm, and none in

the AXS-05 arm. 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.

“We are excited by the rapid and substantial effect of AXS-05 on agitation in patients with Alzheimer’s disease observed in this trial,” said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. “The positive ADVANCE-1 Phase 2/3 trial represents a potentially important milestone for Alzheimer’s disease patients, their caregivers, and physicians, particularly given the lack of approved treatments for, and the serious and distressing nature of, Alzheimer’s disease agitation. We look forward to discussing these data with the FDA. These results underscore the potentially broad applicability of the pharmacology of AXS-05, which has also resulted in positive pivotal trial results in major depressive disorder. We remain on track to submit an NDA for AXS-05 for the treatment of major depressive disorder, as well as for our AXS-07 product candidate for the acute treatment of migraine, both in the fourth quarter of this year.”

“With the ADVANCE-1 trial, AXS-05 has now demonstrated efficacy in Alzheimer’s disease agitation, depression, and smoking cessation trials. Additionally, AXS-05 has shown a rapid onset of action in both Alzheimer’s disease agitation and depression against both active and placebo comparators," said Cedric O’Gorman, MD, Senior Vice President of Clinical Development and Medical Affairs of Axsome. "Axsome is committed to accelerating the innovation of effective and safe medicines for the many people underserved by currently available CNS therapies, as exemplified by our late-stage pipeline comprising five product candidates in development for seven different indications.”

AXS-05 is a novel, oral, non-competitive NMDA receptor antagonist with activity on other neurotransmitter systems (sigma-1, serotonin, norepinephrine, dopamine) that have been implicated in the cognitive and behavioral abnormalities in Alzheimer’s disease [2,5,6]. AXS-05 may therefore enhance synaptic transmission and improve the functioning of cortical circuits in patients with Alzheimer’s disease and agitation. Microglial activation is believed to contribute to neuronal damage in neurodegenerative diseases including Alzheimer’s disease [7]. *In vitro* pharmacological actions of AXS-05 include inhibition of microglial activation [8]. AXS-05 is covered by more than 42 issued U.S. and international patents providing protection out to 2034, and Axsome maintains worldwide rights.

Detailed study results will be submitted for presentation at upcoming medical meetings and for publication.

Summary of Topline Results of the ADVANCE-1 Trial

Effect on Agitation

- AXS-05 was associated with a statistically significant mean reduction from baseline in the Cohen Mansfield Agitation Inventory (CMAI) total score of 15.4 points for AXS-05 compared to 11.5 points for placebo (p=0.010), and 10.0 points for bupropion (p<0.001).
- The improvements on the CMAI represent a reduction in agitation from baseline of 48% for AXS-05 compared to 38% for placebo.
- AXS-05 demonstrated clinical response on the CMAI, defined as a 30% or greater improvement from baseline, in 73% of treated patients compared to 57% for placebo (p=0.005).
- AXS-05 demonstrated superiority to placebo on clinicians’ global assessments of change measured using the modified Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC) (p=0.036).

Time Course of Effect on Agitation

- AXS-05 numerically separated from placebo at Week 2 with a mean reduction from baseline in the CMAI total score of 11.5 points for AXS-05 compared to 8.7 points for placebo (p=0.069).
- AXS-05 demonstrated a statistically significant mean reduction from baseline in the CMAI total score of 13.8 points for AXS-05 compared to 9.7 points for placebo at Week 3 (p=0.007), with statistical significance for this measure maintained thereafter.

Safety and Tolerability

- AXS-05 was generally well tolerated in the trial.
- The most commonly reported adverse events in the AXS-05 arm were somnolence (8.2%, 4.1%, 3.2%, respectively), dizziness (6.3% for AXS-05 versus 10.2% for bupropion and 3.2% for placebo), and diarrhea (4.4%, 6.1%, 4.4%, respectively).
- The rates of discontinuation due to adverse events were 1.3%, 2.0%, and 1.3% in the AXS-05, bupropion, and placebo arms, respectively. Serious adverse events were reported in 3.1% of patients treated with AXS-05 compared to 8.2% of bupropion- and 5.7% of placebo-treated patients, and were deemed not to be related to study drug. There was one death in the placebo arm, one in the bupropion arm, and none in the AXS-05 arm.
- 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 cognitive function.
- Treatment with AXS-05 was not associated with sedation.

Conference Call Information

Axsome will host a conference call and webcast with slides today at 8:00 AM Eastern to discuss the topline results of the ADVANCE-1 trial of AXS-05 in Alzheimer’s disease agitation. To participate in the live conference call, please dial (844) 698-4029 (toll-free domestic) or (647) 253-8660 (international), and use the passcode 9617816. The live webcast can be accessed on the “Webcasts & Presentations” page of the “Investors” section of the Company’s website at axsome.com. A replay of the webcast will be available for approximately 30 days following the live event.

About the ADVANCE-1 Trial

ADVANCE-1 (Addressing Dementia via Agitation-Centered Evaluation 1) was a Phase 2/3 randomized, double-blind, controlled, multicenter, U.S. trial to evaluate the efficacy and safety of AXS-05 in patients with agitation associated with Alzheimer's disease. Patients with a diagnosis of probable Alzheimer's disease and clinically meaningful agitation associated with their disease were randomized, initially in a 1:1:1 ratio, to receive AXS-05 (dextromethorphan/bupropion, dose escalated from 30 mg/105 mg once daily to 45 mg/105 mg twice daily), bupropion (dose escalated from 105 mg once daily to 105 mg twice daily), or matching placebo, for 5 weeks. An independent data monitoring committee performed an interim futility analysis and recommended no further randomization to the bupropion arm. Subsequently, patients were randomized in a 1:1 ratio to receive AXS-05 or placebo. Total patients randomized were 159, 49, and 158 to the AXS-05, bupropion, and placebo arms, respectively. The mean Cohen-Mansfield Agitation Inventory (CMAI) total scores at baseline were 60.8, 66.1, and 59.3, respectively for the AXS-05, bupropion, and placebo groups. 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 of the study was the change from baseline in the CMAI total score at Week 5. P-values were calculated based on least square mean estimates.

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 is a novel, oral, patent-protected, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of Alzheimer's disease agitation, major depressive disorder, and other central nervous system (CNS) disorders. AXS-05 consists of a proprietary formulation and dose of dextromethorphan and bupropion and utilizes Axsome's metabolic inhibition technology. The dextromethorphan component of AXS-05 is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, a sigma-1 receptor agonist, an inhibitor of the serotonin and norepinephrine transporters, a nicotinic acetylcholine receptor antagonist, and an inhibitor of microglial activation. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. AXS-05 is covered by more than 42 issued U.S. and international patents which provide protection out to 2034. AXS-05 has been granted U.S. Food and Drug Administration (FDA) Breakthrough Therapy designation for the treatment of MDD, as well as Fast Track designations for the treatment of Alzheimer's disease agitation and treatment resistant depression. AXS-05 is not approved by the FDA.

About Axsome Therapeutics, Inc.

Axsome Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders for which there are limited treatment options. For the many people facing unsatisfactory treatments for CNS disorders, Axsome accelerates the invention and adoption of life-changing medicines. Axsome's core CNS product candidate portfolio includes five clinical-stage candidates, AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14. AXS-05 is being developed for major depressive disorder (MDD), treatment resistant depression (TRD), Alzheimer's disease (AD) agitation, and as treatment for smoking cessation. AXS-07 is being developed for the acute treatment of migraine. AXS-12 is being developed for the treatment of narcolepsy. AXS-14 is being developed for fibromyalgia. AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14 are investigational drug products not approved by the FDA. For more information, please visit the Company's website at axsome.com. The Company may occasionally disseminate material, nonpublic information on the company website.

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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 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, FDA’s agreement with the Company’s discontinuation of the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee’s recommendations); the potential for the MOMENTUM clinical trial to provide a basis for approval of AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment; 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 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. The data disclosed in this press release are considered topline data and subject to further statistical review and the final results may vary.

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