Axsome Therapeutics Announces Successful Completion and Results of Phase 3 Clinical Program of AXS-05 in Alzheimer's Disease Agitation

December 30, 2024

ACCORD-2 Phase 3 trial in Alzheimer's disease agitation achieves primary endpoint compared to placebo (p=0.001, time to relapse)

ACCORD-2 Phase 3 trial achieves key secondary endpoint compared to placebo (p=0.001, prevention of relapse of Alzheimer's disease agitation)

AXS-05 reduced worsening of Alzheimer's disease overall compared to placebo in ACCORD-2 Phase 3 trial (p<0.001, CGI-S Alzheimer's disease overall clinical status)

ADVANCE-2 trial did not demonstrate statistical significance on primary endpoint; numerically greater improvements with AXS-05 over placebo (primary and secondary endpoints)

Long-term safety trial completed with required number of patients treated for 6 and 12 months

AXS-05 was well tolerated in controlled and long-term trials, and was not associated with death, increased risk of falls, cognitive decline, or sedation

Four completed pivotal, Phase 3, placebo-controlled trials support efficacy and safety of AXS-05 in Alzheimer's disease agitation

The Company plans to submit a New Drug Application (NDA) to the FDA in 2H 2025

Conference call and webcast to take place today at 8:00 AM Eastern

NEW YORK, Dec. 30, 2024 (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 the successful completion of its Phase 3 clinical program evaluating AXS-05 (dextromethorphan-bupropion), a novel, oral, investigational NMDA receptor antagonist, sigma-1 agonist, and aminoketone CYP2D6 inhibitor, in Alzheimer's disease agitation, and results of the ACCORD-2, ADVANCE-2, and long-term safety trials in this indication.

The ACCORD-2 Phase 3 trial achieved the primary endpoint with AXS-05 statistically significantly delaying the time to relapse of agitation, assessed by the Cohen-Mansfield Agitation Inventory (CMAI) total score, in patients with Alzheimer's disease compared to placebo (hazard ratio for time to relapse of 0.276, p=0.001), demonstrating a 3.6-fold lower risk of relapse compared to placebo. AXS-05 also met the key secondary endpoint (relapse prevention, p=0.001). Further, AXS-05 reduced worsening for overall Alzheimer's disease severity compared to placebo, as assessed by the Clinical Global Impression of Severity (CGI-S) for Alzheimer's disease (p<0.001).

The ADVANCE-2 Phase 3 trial did not demonstrate statistical significance for the primary endpoint, change in the CMAI total score from baseline to Week 5 (CMAI reductions of 13.8 and 12.6 points for AXS-05 and placebo, respectively). However, results for the primary and nearly all secondary endpoints numerically favored AXS-05 over placebo.

AXS-05 was safe and well tolerated in both controlled studies. The long-term safety and tolerability of AXS-05 was also evaluated in more than 300 subjects treated for at least 6 months and more than 100 subjects treated for at least 12 months. In the controlled and long-term studies in subjects with Alzheimer's disease, AXS-05 was not associated with increased risk of falls, cognitive decline, or sedation. In the clinical program for AXS-05 in Alzheimer's disease agitation, there have been no deaths in subjects receiving AXS-05.

AXS-05 has now demonstrated statistically significant efficacy compared to placebo in three completed pivotal Phase 3 trials (ADVANCE-1, ACCORD-1 and ACCORD-2), with supportive efficacy and controlled safety results in a fourth trial (ADVANCE-2). Axsome plans to submit an NDA for AXS-05 in Alzheimer's disease agitation to the FDA in the second half of 2025, based on the efficacy and safety data from the above controlled and long-term studies. AXS-05 has been granted Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation.

Jeffrey Cummings, MD, ScD, Vice Chair of Research, UNLV Department of Brain Health commented, "Agitation is one of the most troubling and consequential aspects of Alzheimer's disease, poses significant challenges to both the patient and their family, and represents a high unmet need. The robust, clinically meaningful efficacy results of the ACCORD-2 trial are consistent with the statistically significant results of the previously completed ADVANCE-1 and ACCORD-1 Phase 3 trials of AXS-05. The improvement in overall Alzheimer's disease severity with AXS-05 in the ACCORD-2 trial is noteworthy. Importantly, short and long-term treatment with AXS-05 was well tolerated and not associated with increased mortality, risk of falls, sedation, or cognitive decline. Taken together, results from this comprehensive Phase 3 program encompassing distinct clinical trial designs strongly support the potential for AXS-05 to become an important treatment for patients living with Alzheimer's disease agitation."

Herriot Tabuteau, MD, CEO of Axsome Therapeutics, added, "We are very pleased with the successful completion of the planned Phase 3 clinical trial program of AXS-05 in the treatment of Alzheimer's disease agitation. With the strong results of the ACCORD-2 trial, AXS-05 has now demonstrated substantial and statistically significant improvements in Alzheimer's disease agitation across three pivotal, Phase 3, placebo-controlled trials,

underscoring its potential to provide meaningful benefit to patients living with this condition and their families. The improvements in the AXS-05 arm relative to placebo in ADVANCE-2 did not reach statistical significance. However, we are pleased with the very positive controlled safety data from this trial which will be an essential part of our planned NDA submission of AXS-05 in Alzheimer's disease agitation, which is targeted for the second half of 2025."

Summary of Topline Results of the ACCORD-2 Phase 3 Trial

ACCORD-2 was a double-blind, placebo-controlled, randomized withdrawal trial of AXS-05 in Alzheimer's disease patients with agitation, consisting of an open-label AXS-05 treatment period, and a randomized, double-blind treatment period. Patients who achieved a sustained clinical response with open-label AXS-05 were then randomized into the double-blind treatment period to either continue on AXS-05 or to switch to placebo.

Open-Label AXS-05 Treatment Period

A total of 295 patients were treated with open-label AXS-05 for up to 12 months and assessed for efficacy. The mean CMAI total score was 73.3 at baseline.

- Treatment with AXS-05 was associated with a mean reduction from baseline in the CMAI total score of 20.4 points at Week 6, representing a 46% reduction from the mean baseline score.
- Clinical response on the CMAI (defined as ≥30% reduction from baseline) after treatment with AXS-05 was achieved by 69% of patients at Week 6, after treatment with AXS-05.
- Improvement in Alzheimer's disease agitation, assessed using the clinician rated modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC), was achieved by 78% of patients at Week 6, after treatment with AXS-05.
- Improvement in Alzheimer's disease agitation, assessed using the caregiver rated Patient Global Impression of Change (PGI-C), was achieved by 71% of patients at Week 4, and 78% of patients at Week 8, after treatment with AXS-05.
- Of the patients treated for at least 8 weeks, 70% experienced a sustained clinical response and were randomized in the double-blind period.

Double-Blind Randomized Period

A total of 167 patients were randomized, 83 to continued treatment with AXS-05, and 84 switched to placebo. The mean CMAI total scores at randomization were 44.3 and 45.4 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 0.276, p=0.001), demonstrating a 3.6-fold lower risk of relapse compared to placebo.
- AXS-05 met the key secondary endpoint by substantially and statistically significantly preventing relapse of Alzheimer's disease agitation as compared to placebo, with 8.4% of AXS-05 patients relapsing versus 28.6% of patients switched to placebo (p=0.001).
- AXS-05 substantially and statistically significantly prevented worsening of severity of Alzheimer's disease agitation as compared to placebo, with 20.5% of AXS-05 patients worsening on the CGI-S for agitation versus 41.7% of patients switched to placebo (p=0.004).
- AXS-05 substantially and statistically significantly prevented worsening of severity of Alzheimer's disease overall as compared to placebo, with 13.3% of AXS-05 patients worsening on the CGI-S for Alzheimer's disease overall clinical status versus 39.3% of patients switched to placebo (p<0.001).

The overall rates of adverse events in the double-blind period were 29.3% in the AXS-05 group and 32.1% in the placebo group, with no individual adverse events occurring in more than 3.7% of subjects. Two subjects (2.4%) in the AXS-05 group experienced falls, only one which was deemed related to study medication. There were two serious adverse events in the double-blind period (cellulitis and urinary retention) both of which occurred in the placebo group. Discontinuations in the double-blind period due to adverse events were low (0% for AXS-05 and 1.2% for placebo).

There were no deaths in the ACCORD-2 trial, and AXS-05 was not associated with sedation or cognitive decline as assessed by the Mini-Mental State Examination (MMSE).

Summary of Topline Results of the ADVANCE-2 Phase 3 Trial

The ADVANCE-2 trial was a double-blind, placebo-controlled, parallel group trial of AXS-05 in Alzheimer's disease patients with agitation. A total of 408 patients were randomized in a 1:1 ratio to treatment with AXS-05 or placebo, for 5 weeks.

- The study did not demonstrate statistical significance for the primary endpoint, change in the CMAI total score from baseline to Week 5 (CMAI reductions of 13.8 and 12.6 points for AXS-05 and placebo, respectively).

- Results of the primary endpoint and almost all secondary endpoints numerically favored AXS-05 over the placebo group.

The overall rates of adverse event in ADVANCE-2 were 26.0% in the AXS-05 group and 21.6% in the placebo group. The most common adverse events were dizziness (5.9% for AXS-05 and 1.5% for placebo), and headache (4.4% for AXS-05 and 3.4% placebo). One subject (0.5%) each in the AXS-05 and placebo groups experienced falls, which was deemed not related to study medication for the subject in the AXS-05 group. Two subjects in the AXS-05 group reported three serious adverse events, none of which were deemed related to study drug (asthenia, urinary tract infection, cerebrovascular accident). Discontinuation due to adverse events were low (1.5% for AXS-05 and 0% for placebo).

In the ADVANCE-2 trial, there were no deaths and AXS-05 was not associated with sedation or cognitive decline as assessed by the MMSE.

Summary of Long-Term Safety

A total of 456 subjects were treated for up to 12 months with AXS-05 in the long-term open-label safety trial. AXS-05 was well tolerated with long-term dosing, with a safety profile consistent with the short-term efficacy and safety trials and no new safety signals identified.

The overall rate of adverse events during the up to 12-month treatment period was 39.9%, with headache (5.5%) being the only adverse event occurring in ≥5% of subjects. The rate of falls over the up to 12-month treatment period was 3.1%, with only 0.2% deemed related to study medication. The rate of serious adverse events during the up to 12-month treatment period was 2.6%, none of which were deemed related to study drug. Discontinuations due to adverse events with long-term dosing were low (0.7%).

There were no deaths and AXS-05 was not associated with sedation or cognitive decline as assessed by the MMSE.

Overall Phase 3 Clinical Development Program

The comprehensive clinical development program of AXS-05 in Alzheimer's disease agitation includes four completed pivotal, Phase 3, placebo-controlled trials that support the efficacy of AXS-05 in this indication:

- ADVANCE-1 – achieved primary endpoint (p=0.010)
- ADVANCE-2 – primary endpoint not statistically significant
- ACCORD-1 – achieved primary endpoint (p=0.014)
- ACCORD-2 – achieved primary endpoint (p=0.001)

The long-term safety of AXS-05 in Alzheimer's disease agitation has been demonstrated in over 300 patients treated for at least 6 months, and over 100 patients treated for at least 12 months.

Axsome plans to submit an NDA for AXS-05 in Alzheimer's disease agitation to the FDA in the second half of 2025, based on the efficacy and safety data from these studies.

AXS-05 was granted Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation in June 2020 based on positive results from the pivotal ADVANCE-1 trial. 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.

Conference Call Information

Axsome will host a conference call and webcast today at 8:00 a.m. Eastern Time to discuss the topline results of the ADVANCE-2 and ACCORD-2 Phase 3 trials of AXS-05 in Alzheimer's disease agitation. Dr. Jeffrey Cummings, Vice Chair of Research, UNLV Department of Brain Health, will join the call and will be available to answer questions during the Q&A session. To participate in the live conference call, please dial (877) 405-1239 (toll-free domestic) or +1 (201) 389-0851 (international). A live webcast of the conference call can be access on the "Webcasts & Presentations" page of the "Investors" section of the Company's website at axsome.com. A replay of the conference call will be available for approximately 30 days following the live event.

About the ADVANCE-2 Trial

ADVANCE-2 (Addressing Dementia via Agitation-Centered Evaluation 2) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, 5-week parallel-group trial. The primary endpoint was the change from baseline in the CMAI total score at Week 5. The minimum score on the CMAI is 29, corresponding to the total absence of symptoms, with higher scores corresponding to greater agitation.

A total of 408 patients with a diagnosis of probable Alzheimer's disease (AD) and clinically meaningful agitation associated with their AD were enrolled in the trial. Patients were randomized 1:1 to receive AXS-05 (dextromethorphan/bupropion, dose escalated from 30 mg/105 mg once daily to 45 mg/105 mg twice daily) or matching placebo for 5 weeks.

About the ACCORD-2 Trial

ACCORD-2 (Assessing Clinical Outcomes in Alzheimer's Disease Agitation 2) was a multicenter Phase 3 trial consisting of an open-label treatment period followed by a 26-week, double-blind, placebo-controlled, randomized withdrawal period. The primary endpoint was the time from randomization to relapse of AD agitation calculated by Kaplan-Meier estimates and the hazard ratio. The key secondary endpoint was the percentage of patients who relapsed compared to placebo.

A total of 167 patients, who rolled over from the open-label extension trial of AXS-05, experienced a sustained clinical response with AXS-05 and were 1:1 randomized to continue AXS-05 (n=83) or to switch to placebo (n=84). Treatment was continued until either a relapse of agitation or the end of the 26-week double-blind period, whichever occurred first. The mean CMAI total score at baseline study entry was 73.3. The mean CMAI total scores at

randomization for the AXS-05 and placebo groups were 44.3 and 45.4, respectively.

About Alzheimer's Disease Agitation

Alzheimer's disease (AD) is the most common form of dementia, affecting approximately 7 million people in the United States.[1] Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, verbal and physical aggressiveness, disruptive irritability, and disinhibition.[1,2] AD agitation has been associated with accelerated cognitive decline, increased caregiver burden, earlier nursing home placement, and increased mortality.[3]

About AXS-05

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 agonist, and aminoketone CYP2D6 inhibitor under development for the treatment of Alzheimer's disease (AD) agitation and smoking cessation. 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 to at least 2043. AXS-05 was granted U.S. FDA Breakthrough Therapy designation for the treatment of Alzheimer's disease agitation in June 2020.

About Axsome Therapeutics

Axsome Therapeutics is a biopharmaceutical company leading a new era in the treatment of central nervous system (CNS) conditions. We deliver scientific breakthroughs by identifying critical gaps in care and develop differentiated products with a focus on novel mechanisms of action that enable meaningful advancements in patient outcomes. Our industry-leading neuroscience portfolio includes FDA-approved treatments for major depressive disorder and excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea and multiple late-stage development programs addressing a broad range of serious neurological and psychiatric conditions that impact over 150 million people in the United States. Together, we are on a mission to solve some of the brain's biggest problems so patients and their loved ones can flourish. For more information, please visit the Company's website at www.axsome.com.

Forward Looking Statements

Certain matters discussed in this press release are "forward-looking statements". The Company 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 the Company's Sunosi® and Auvelity® products and the success of the Company's efforts to obtain any additional indication(s) with respect to solriamfetol and/or AXS-05; the Company's ability to maintain and expand payer coverage; the success, timing and cost of the Company's ongoing clinical trials and anticipated clinical trials for the Company's current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including the Company's ability to fully fund the Company's disclosed clinical trials, which assumes no material changes to the Company's currently projected revenues or expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of the Company's ongoing clinical trials and/or data readouts, 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 the Company's current product candidates, including statements regarding the ability of the ACCORD and ADVANCE clinical trials to support the filing of an NDA for Alzheimer's disease agitation; the Company's ability to fund additional clinical trials to continue the advancement of the Company's product candidates; the timing of and the Company's ability to obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory authority approval of, or other action with respect to, the Company's product candidates, including statements regarding the timing of any NDA submission; 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 the Company's 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, if approved, and the potential impact on the Company's anticipated cash runway; the Company's ability to convert sales to recognized revenue and maintain a favorable gross to net sales; unforeseen circumstances or other disruptions to normal business operations arising from or related to domestic political climate, geo-political conflicts or a global pandemic 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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Source: Axsome Therapeutics, Inc.