Axsome Therapeutics Announces AXS-12 Achieves Primary Endpoint in CONCERT Phase 2 Trial in Narcolepsy

December 3, 2019

Demonstrated statistically significant reduction in cataplexy attacks compared to placebo (p<0.001 on primary endpoint)

Reduced excessive daytime sleepiness compared to placebo (p=0.003 on ESS; p<0.001 on inadvertent naps)

Improved cognitive function compared to placebo (p<0.001)

Improved sleep quality (p=0.007) and sleep-related symptoms compared to placebo

Positive results support initiation of Phase 3 trials, planned in 2020

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

NEW YORK, Dec. 03, 2019 (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-12 (reboxetine) met the prespecified primary endpoint and significantly reduced the number of cataplexy attacks as compared to placebo in patients with narcolepsy in the CONCERT Phase 2 trial. AXS-12 also significantly reduced excessive daytime sleepiness (EDS), and improved cognitive function, sleep quality and sleep-related symptoms. Narcolepsy is a debilitating, neurological condition characterized by EDS and cataplexy, a sudden loss of muscle tone triggered by strong emotions. AXS-12 has been granted Orphan Drug Designation by the U.S. Food and Drug Administration (FDA) for the treatment of narcolepsy. CONCERT was a Phase 2, randomized, double-blind, placebo-controlled, crossover, multicenter, U.S. trial in which 21 patients with a diagnosis of narcolepsy with cataplexy were all treated with orally administered AXS-12 for 2 weeks, and with placebo for 2 weeks, with the treatment periods separated by 1 week of down-titration and washout.

AXS-12 met the prespecified primary endpoint by demonstrating a highly statistically significant reduction from baseline in the mean weekly number of cataplexy attacks, averaged for the 2-week treatment period (overall treatment effect), as compared to placebo (p<0.001). At Week 2, AXS-12 demonstrated a mean reduction of 14.6 cataplexy attacks per week compared to a reduction of 2.6 attacks per week for placebo (p=0.002), representing mean reductions of 48.8% and 8.6% from baseline, respectively. The proportion of patients achieving a 50% or greater reduction in the weekly number of cataplexy attacks was 76.2% for AXS-12, compared to 30.0% for placebo (p=0.003) at Week 2. The improvement in cataplexy was rapid with AXS-12 demonstrating significant benefit over placebo as early as Week 1 (p<0.001).

AXS-12 significantly improved EDS symptoms compared to placebo, as measured by the Epworth Sleepiness Scale (ESS) and by the frequency of inadvertent naps. The improvement on the ESS with AXS-12 treatment was twice that observed with placebo, with reductions from baseline in the ESS score of 6.0 and 3.1, respectively for AXS-12 and placebo (p=0.003). AXS-12 treatment resulted in a 31.8% mean reduction from baseline in the average weekly number of inadvertent naps versus a 5.3% mean reduction for placebo (p<0.001) at Week 2. The improvement in frequency of inadvertent naps was rapid with AXS-12 demonstrating significant benefit over placebo as early as Week 1 (p=0.038).

AXS-12 significantly improved cognitive function compared to placebo over the 2-week treatment period as measured by the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire (NSAQ), which was assessed daily (p<0.001). For this assessment, patients rated their ability to concentrate on a 5-point scale (1=very good to 5=very poor). At the end of treatment, 42.9% of patients had an ability to concentrate that was “good” to “very good” with AXS-12 treatment, compared to 25.0% of patients with placebo, and 0% of patients at baseline. The improvement in the ability to concentrate was rapid with AXS-12 demonstrating significant improvement over placebo as early as Week 1 (p=0.007).

AXS-12 significantly improved sleep quality, as measured by overall improvement and by number of awakenings at night, and reduced sleep-related symptoms, as compared to placebo. AXS-12 treatment resulted in 45.0% of patients reporting improved sleep quality versus 5.3% of patients with placebo (p=0.007). AXS-12 treatment resulted in 30.0% of patients reporting a reduction in the number of awakenings at night versus 5.3% of patients with placebo (p=0.044). AXS-12 treatment also resulted in greater proportions of patients with reductions in sleep paralysis episodes, and in hypnagogic hallucinations, as compared to placebo (p=ns).

“Narcolepsy is a neurological disorder that interferes with mental and social functioning, increases work and driving related accidents, and results in a nearly two-fold higher mortality rate,” said Dr. Michael J. Thorpy, Professor of Neurology at Albert Einstein College of Medicine. “Medications that have the potential to reduce cataplexy symptoms, promote wakefulness, and enhance cognitive function, such as AXS-12, if borne out in Phase 3 trials, could provide new treatment options for patients living with this debilitating disorder.”

AXS-12 was safe and well tolerated. There were no serious adverse events reported in the trial, and no discontinuations due to adverse events. The overall percentage of patients experiencing adverse events was 42.9% with AXS-12 and 40.0% with placebo, with the most commonly reported adverse events with AXS-12 treatment being anxiety, constipation, and insomnia. The completion rate was 91% for patients randomized to treatment sequence 1 (AXS-12 followed by placebo) and 100% for those randomized to sequence 2 (placebo followed by AXS-12).

“We are very pleased with the results of the CONCERT trial, which demonstrated a strong effect of AXS-12 on both cataplexy and excessive daytime sleepiness symptoms, as well as on cognitive function, in narcolepsy patients. The improvement in the ability to concentrate with AXS-12 is especially relevant because the cognitive impairment associated with narcolepsy is one of the most distressing aspects of the disease for patients, as highlighted in the FDA’s The Voice of the Patient report on Narcolepsy,” said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. “Based on these positive results, Axsome intends to initiate Phase 3 trials of AXS-12 in 2020 with the goal of bringing this differentiated experimental medicine to narcolepsy patients as soon as possible.”

“The CONCERT trial exemplifies Axsome’s commitment to accelerating the innovation of effective treatments for difficult-to-treat CNS disorders such as narcolepsy. Our approach uses innovative clinical trial designs to effectively assess the potential of our product candidates to address unmet medical needs,” said Cedric O’Gorman, MD, Senior Vice President of Clinical Development and Medical Affairs of Axsome. “Existing treatment options for narcolepsy are few, do not address all key symptoms, may not be well tolerated, and are mostly controlled substances. If successfully developed, AXS-12 may overcome these limitations and could make it a candidate as foundational therapy to meaningfully improve the lives of the many narcolepsy patients.”

Axsome plans to present the detailed results of the CONCERT trial at upcoming scientific meetings.

Summary of Topline Results of the CONCERT Trial

Effect on Cataplexy

- AXS-12 was associated with a statistically significant reduction from baseline in the mean weekly number of cataplexy attacks, averaged for the 2-week treatment period, as compared to placebo ($p<0.001$).
- At Week 2, AXS-12 was associated with a statistically significant mean reduction from baseline in the weekly number of cataplexy attacks of 14.6 attacks per week for AXS-12 compared to a reduction of 2.6 attacks for placebo ($p=0.002$), representing mean reductions from baseline of 48.8% and 8.6%, respectively.
- The proportion of patients achieving a 50% or greater reduction in the weekly number of cataplexy attacks was 76.2% for AXS-12, compared to 30.0% for placebo ($p=0.003$) at Week 2.
- The effect of AXS-12 on cataplexy was rapid with AXS-12 demonstrating a statistically significant improvement in the frequency of cataplexy as compared to placebo as early as Week 1 ($p<0.001$).

Effect on Excessive Daytime Sleepiness (EDS)

- AXS-12 was associated with a statistically significant mean reduction in Epworth Sleepiness Scale (ESS) score from baseline as compared to placebo, with mean reductions of 6.0 and 3.1 points, respectively for AXS-12 and placebo ($p=0.003$).
- AXS-12 was associated with a statistically significant reduction from baseline in the weekly number of inadvertent naps as compared to placebo, with a mean reduction of 31.8% for AXS-12 versus 5.3% for placebo ($p<0.001$), at Week 2.
- The improvements in EDS symptoms were rapid with AXS-12 demonstrating significantly greater reductions than placebo in the number of inadvertent naps at Week 1 ($p=0.038$).

Effect on Cognitive Function

- AXS-12 significantly improved cognitive function compared to placebo over the 2-week treatment period as measured by the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire (NSAQ), which was assessed daily ($p<0.001$).
- At the end of treatment, 42.9% of patients had an ability to concentrate that was “very good” or “good” with AXS-12 treatment, compared to 25.0% of patients with placebo, and 0% of patients at baseline.
- The improvement in the ability to concentrate was rapid with AXS-12 demonstrating significant improvement over placebo at Week 1 ($p=0.007$).

Effect on Sleep Quality and Sleep-related Symptoms

- AXS-12 treatment resulted in 45.0% of patients reporting improved sleep quality versus 5.3% of patients with placebo ($p=0.007$).
- AXS-12 treatment resulted in 30.0% of patients reporting a reduction in the number of awakenings at night versus 5% of patients with placebo ($p=0.044$).
- AXS-12 treatment also resulted in greater proportions of patients with reductions in sleep paralysis episodes (55.0% vs. 26.3%), and in hypnagogic hallucinations (40.0% vs. 26.3%), as compared to placebo (p=ns).

Safety and Tolerability

- AXS-12 was safe and well tolerated. There were no serious adverse events, and no discontinuations due to adverse events.

- The overall rate of adverse events was 42.9% for patients treated with AXS-12 and 40.0% for patients treated with placebo, with the most commonly reported adverse events with AXS-12 treatment being anxiety, constipation, and insomnia.

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 CONCERT trial of AXS-12 in narcolepsy. To participate in the live conference call, please dial (844) 698-4029 (toll-free domestic) or (647) 253-8660 (international), and use the passcode 6872588. 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 CONCERT Trial

CONCERT (Clinical Outcomes in Narcolepsy and Cataplexy: An Evaluation of Reboxetine Treatment) was a Phase 2, double-blind, randomized, placebo-controlled, crossover, multicenter trial of AXS-12 in patients with narcolepsy. A total of 21 patients with a diagnosis of narcolepsy with cataplexy were treated for 2 weeks with AXS-12 or with placebo, followed by a crossover to the other treatment after a 1-week down-titration and washout period. AXS-12 was administered orally twice daily, with a total daily dose of 8 mg for Week 1 which was escalated to 10 mg for Week 2. Patients were randomized in a 1:1 ratio either to treatment with AXS-12 followed by placebo (sequence 1), or to treatment with placebo followed by AXS-12 (sequence 2). The average number of cataplexy attacks at baseline was 30. Key assessments were made daily using an electronic diary. The prespecified primary endpoint was the change in the weekly number of cataplexy attacks, averaged over the 2-week treatment period (overall treatment effect). Secondary endpoints included changes in the number of inadvertent naps, cognition, and Epworth Sleepiness Scale. Cognition was assessed using the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire, a patient reported outcome measure. This item is rated on 5-point scale (1=very good to 5=very poor). All analyses were conducted on an intent-to-treat basis.

About Narcolepsy

Narcolepsy is a serious and debilitating neurological condition that causes dysregulation of the sleep-wake cycle and is characterized clinically by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep. Narcolepsy afflicts an estimated 185,000 individuals in the U.S. Cataplexy is seen in an estimated 70% of narcolepsy patients and is a sudden reduction or loss of muscle tone while a patient is awake, typically triggered by strong emotions such as laughter, fear, anger, stress, or excitement. Narcolepsy interferes with cognitive, psychological, and social functioning, increases the risk of work- and driving-related accidents, and is associated with a 1.5 fold higher mortality rate. Depression is reported in up to 57% of patients.

About AXS-12

AXS-12 (reboxetine) is a highly selective and potent norepinephrine reuptake inhibitor for the treatment of narcolepsy. AXS-12 modulates noradrenergic activity to promote wakefulness, maintain muscle tone and enhance cognition. AXS-12 is an investigational drug product 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. Axsome's core CNS product candidate portfolio includes four clinical-stage candidates, AXS-05, AXS-07, AXS-09, and AXS-12. AXS-05 is currently in a Phase 3 trial in treatment resistant depression (TRD), a Phase 3 trial in major depressive disorder (MDD), and a Phase 2/3 trial in agitation associated with Alzheimer's disease (AD). AXS-05 is also being developed for smoking cessation treatment. AXS-07 is currently in two Phase 3 trials for the acute treatment of migraine. AXS-12 is currently in a Phase 2 trial in narcolepsy. AXS-05, AXS-07, AXS-09, and AXS-12 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.

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 plan to discontinue the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee's recommendations); the potential for the ASCEND clinical trial 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 and

the Company's current expectations regarding its plans for future equity financings prior to the readout from its Phase 3 trials; 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.

Axsome Contact:
Mark Jacobson
Senior Vice President, Operations
Axsome Therapeutics, Inc.
200 Broadway, 3rd Floor
New York, NY 10038
Tel: 212-332-3243
Email: mjacobson@axsome.com
www.axsome.com

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