Axsome Therapeutics Announces AXS-12 Achieves Primary Endpoint in the SYMPHONY Phase 3 Trial in Narcolepsy

March 25, 2024

AXS-12 statistically significantly reduced cataplexy attacks compared to placebo (p=0.018, primary endpoint)

AXS-12 achieved statistically significant remission of cataplexy compared to placebo (p=0.008)

AXS-12 statistically significantly reduced excessive daytime sleepiness (EDS) severity compared to placebo (p=0.027, CGI-S for EDS)

AXS-12 statistically significantly improved concentration and memory compared to placebo (p=0.004, Cognitive Function items of FOSQ-10)

AXS-12 statistically significantly reduced overall severity of narcolepsy compared to placebo (p=0.007, CGI-S for narcolepsy)

AXS-12 statistically significantly improved overall function and quality of life compared to placebo (p=0.005, FOSQ-10 total score)

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

NEW YORK, March 25, 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 that AXS-12 (reboxetine), a highly selective and potent norepinephrine reuptake inhibitor and cortical dopamine modulator, achieved the primary endpoint and significantly reduced the frequency of cataplexy attacks as compared to placebo in patients with narcolepsy in the SYMPHONY Phase 3 trial. AXS-12 also reduced excessive daytime sleepiness (EDS) severity, improved cognitive function, and reduced overall narcolepsy severity as compared to placebo. SYMPHONY was a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial in which 90 patients with a diagnosis of narcolepsy with cataplexy were randomized to treatment with AXS-12 or placebo for 5 weeks.

“AXS-12 is a novel therapeutic approach to the treatment of narcolepsy as evidenced by the strong clinical results generated from the Phase 3 SYMPHONY trial, including a rapid and significant reduction in cataplexy events compared to placebo,” commented Dr. Michael Thorpy, Director of the Sleep-Wake Disorders Center at the Montefiore Medical Center and Professor of Neurology at Albert Einstein College of Medicine. “Despite the existence of multiple approved narcolepsy treatments, significant unmet need still exists given the high rates of persistent symptoms reported by patients. Based on the concurrent improvements observed on cataplexy, severity of excessive daytime sleepiness, cognition and overall function, I believe AXS-12 represents a meaningful enhancement to the treatment armamentarium for narcolepsy patients and clinicians and will be a welcome treatment option in our fight against the devastating impact of narcolepsy on patients and their loved ones.”

AXS-12 met the primary endpoint by demonstrating a substantial and statistically significant reduction from baseline in weekly cataplexy attacks compared to placebo at Week 5, with reductions of 83% for AXS-12 and 66% for placebo (p=0.018). AXS-12 rapidly reduced weekly cataplexy attacks, demonstrating at Week 1 a reduction of 56% compared to a reduction of 31% for placebo (p=0.007).

AXS-12 induced remission of cataplexy and increased cataplexy-free days compared to placebo. Remission of cataplexy, defined as a 100% reduction from baseline, was achieved at Week 5 by 33% of AXS-12 treated patients compared to 9.5% of placebo patients (p=0.008). Achievement of remission was rapid, being experienced at Week 2 by 24% of AXS-12 treated patients compared to 4.5% of placebo patients (p=0.008). AXS-12 increased the percentage of cataplexy-free days per week, defined as days with zero cataplexy attacks, to 84.5% at Week 5 compared to 22.6% for placebo (p=0.014).

AXS-12 significantly reduced excessive daytime sleepiness (EDS) severity, assessed by the Clinician Global Impression of Severity (CGI-S) scale for EDS, compared to placebo at Week 5 with mean reductions of 1.8 points for AXS-12 compared to 0.9 points for placebo (p=0.027). Rapid improvement on the CGI-S for EDS was seen as early as Week 1 compared to placebo (p=0.006). AXS-12 concurrently improved EDS and cataplexy as compared to placebo. Concurrent EDS and cataplexy response was achieved at Week 5 by 57% of patients treated with AXS-12 compared to 33% of placebo patients (p=0.029). Concurrent EDS and cataplexy response was defined as a ≥30% reduction in inadvertent naps (EDS response), and a ≥50% reduction in cataplexy attacks (cataplexy response).

A decrease in the number of inadvertent naps was experienced by 54% of AXS-12 patients at Week 5 compared to 28% of placebo patients (p=0.016), assessed by the Narcolepsy Symptom Assessment Questionnaire (NSAQ). Improvement on the Epworth Sleepiness Scale (ESS) was numerically greater for AXS-12 than for placebo, with mean reductions from baseline of 4.7 points for AXS-12 compared to 3.4 points for placebo. A ≥3-point improvement from baseline on the ESS was achieved by 60% of AXS-12 patients who had a cataplexy response.

AXS-12 significantly improved concentration and memory as measured by the Cognitive Function Items of the Functional Outcomes of Sleep Questionnaire (FOSQ-10) at Week 5 (p=0.004). AXS-12 concurrently improved cognition and cataplexy as compared to placebo. Concurrent cognitive and cataplexy response was achieved at Week 5 by 41% of patients treated with AXS-12 compared to 17% of placebo patients (p=0.016). Response was defined by an increase in days patients rated their Ability to Concentrate as very good or good (cognitive response), and a ≥50% reduction in

cataplexy attacks (cataplexy response).

AXS-12 improved narcolepsy overall disease condition, and patient function and quality of life. Clinicians reported a rapid and significant reduction in overall narcolepsy severity (CGI-S for narcolepsy overall) for patients treated with AXS-12 compared to placebo at Week 5 (p=0.007), with improvements observed as early as Week 1 (p<0.001). AXS-12 demonstrated significant improvement in overall patient function and quality of life as measured by the FOSQ-10 total score as compared to placebo at Week 5 (p=0.005).

Anxiety and depression, known common narcolepsy co-morbidities, was reported by 45% of study participants at baseline, as assessed by the EuroQol (EQ-5D-5L). Improvement from baseline in the Anxiety/Depression domain of the EQ-5D-5L was achieved by 55% of patients treated with AXS-12 compared to 32% of placebo patients (p=0.146).

"The SYMPHONY Phase 3 trial results confirm the promise and potential of AXS-12 for the treatment of narcolepsy," said Dr. Herriot Tabuteau, CEO of Axsome Therapeutics. "Treatment with AXS-12 resulted in rapid and substantial reduction of cataplexy events, the primary endpoint of the SYMPHONY trial, while evidencing improvement across a range of validated global clinical, patient-reported, quality of life, and functional outcome measures. Collectively, the data generated in SYMPHONY highlight AXS-12's positive therapeutic impact and are consistent with the results from the previously completed positive CONCERT trial. As a next step, we look forward to completing the ongoing open label safety extension trial of AXS-12 as we work to bring this treatment to individuals living with narcolepsy."

AXS-12 was well tolerated in the trial. The most commonly reported adverse events in the AXS-12 arm were dry mouth (n=6), nausea (n=6), and constipation (n=4), which were overall mild to moderate. The rates of discontinuation due to adverse events was low (n=1 in each of AXS-12 and placebo arms). There were no serious adverse events in the trial.

AXS-12 was granted Orphan Drug Designation for the treatment of narcolepsy in October 2018. Orphan Drug Designation is granted to promising drugs intended for the safe and effective treatment of rare diseases, defined as those affecting fewer than 200,000 people in the U.S. This designation may entitle Axsome to a period of seven years of marketing exclusivity in the U.S. upon FDA approval and a waiver of the Company's obligation to pay the FDA application user fees for the product as required by the Prescription Drug User Fee Act. AXS-12 is covered by issued patents providing protection to at least 2039.

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

Summary of Topline Results of the SYMPHONY Trial

Effect on Cataplexy

- AXS-12 demonstrated a substantial and statistically significant reduction from baseline in weekly cataplexy attacks compared to placebo at Week 5, with reductions of 83% for AXS-12 and 66% for placebo (p=0.018).
- AXS-12 demonstrated a statistically significant reduction from baseline in weekly cataplexy attacks compared to placebo at Week 1, with reductions of 56% for AXS-12 and 31% for placebo (p=0.007).
- AXS-12 achieved remission of cataplexy (100% reduction from baseline) at Week 5 in 33% of patients compared to 9.5% of placebo patients (p=0.008).
- Remission at Week 2 was achieved by 24% of AXS-12 treated patients compared to 4.5% of placebo patients (p=0.008).
- AXS-12 increased the percentage of cataplexy free days (days with zero cataplexy attacks) to 84% at Week 5 compared to 22% for placebo (p=0.014).

Effect on Excessive Daytime Sleepiness (EDS)

- AXS-12 significantly reduced EDS severity compared to placebo at Week 5 with mean reductions on the CGI-S for EDS of 1.8 points for AXS-12 compared to 0.9 points for placebo (p=0.027).
- Improvement on the CGI-S for EDS was seen as early as Week 1 compared to placebo (p=0.006).
- Concurrent EDS and cataplexy response was achieved at Week 5 by 57% of patients treated with AXS-12 compared to 33% of placebo patients (p=0.029).
- A reduction in the number of inadvertent naps was experienced by 54% of AXS-12 patients at Week 5 compared to 28% of placebo patients (p=0.016), assessed by the NSAQ.
- Mean reductions from baseline on the ESS were 4.8 points for AXS-12 and 3.4 points for placebo. A ≥3-point improvement from baseline on the ESS was achieved by 60% of AXS-12 patients who had a cataplexy response.

Effect on Cognitive Function

- AXS-12 significantly improved concentration and memory as measured by the Cognitive Function Items of the FOSQ-10 at Week 5 (p=0.004).
- Concurrent cognitive response (increase in days with very good or good Ability to Concentrate) and cataplexy response

was achieved at Week 5 by 41% of patients treated with AXS-12 compared to 17% of placebo patients (p=0.016).

Effect on Narcolepsy Overall, Function and Quality of Life

- AXS-12 treatment resulted in significant reduction in overall narcolepsy severity (CGI-S for narcolepsy overall) compared to placebo at Week 5 (p=0.007).
- Improvement in the CGI-S for narcolepsy overall for AXS-12 compared to placebo was observed as early as Week 1 (p<0.001).
- AXS-12 demonstrated significant improvement in overall patient function and quality of life as measured by the FOSQ-10 total score as compared to placebo at Week 5 (p=0.005).

Anxiety/Depression Comorbidity

- Anxiety and depression was reported by 45% of study participants at baseline, as assessed by the EQ-5D-5L.
- Improvement from baseline in the Anxiety/Depression domain of the EQ-5D-5L was achieved by 55% of patients treated with AXS-12 compared to 32% of placebo patients (p=0.146).

Safety and Tolerability

- AXS-12 was well tolerated in the trial.
- The most commonly reported adverse events in the AXS-12 arm were dry mouth (n=6), nausea (n=6), and constipation (n=4), which were overall mild to moderate.

Conference Call Information

Axsome will host a conference call and webcast today at 8:00 AM Eastern to discuss the topline SYMPHONY study results in narcolepsy. To participate in the live conference call, please dial (877) 405-1239 (toll-free domestic). 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 SYMPHONY Trial

SYMPHONY (Study Evaluating a Mechanistic Approach to Treating Narcolepsy) was a Phase 3, randomized, double-blind, multicenter, placebo-controlled trial to assess the efficacy and safety of AXS-12 in patients with narcolepsy. In all, a total of 90 patients were randomized in a 1:1 ratio to treatment with AXS-12 or placebo for 5 weeks. Participants took either AXS-12 (5 mg) or placebo once daily during Week 1 followed by twice daily dosing during Weeks 2-5. The median number of cataplexy attacks at baseline was 20 and Epworth Sleep Scores were 17.8 at baseline. The prespecified primary endpoint was the change in frequency of weekly cataplexy attacks. Other symptoms of narcolepsy as well as safety and tolerability were assessed throughout the study.

About Narcolepsy

Narcolepsy is a serious and debilitating orphan 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. 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.

About AXS-12

AXS-12 (reboxetine) is a highly selective and potent norepinephrine reuptake inhibitor and cortical dopamine modulator under development for the treatment of narcolepsy. AXS-12 is thought to modulate noradrenergic activity to promote maintain tone during wakefulness, and noradrenergic and cortical dopamine signaling to promote wakefulness and enhance cognition. AXS-12 has been granted U.S. Food and Drug Administration (FDA) Orphan Drug Designation for the treatment of narcolepsy. AXS-12 is covered by issued patents providing protection to at least 2039. AXS-12 is an investigational drug product not approved by the FDA.

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 solriamfetol 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 revenues or expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our 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 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 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 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, if approved, 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 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.

Axsome Contacts:

Investors:
Mark Jacobson
Chief Operating Officer
Axsome Therapeutics, Inc.
One World Trade Center, 22nd Floor
New York, NY 10007
Tel: 212-332-3243
Email: mjacobson@axsome.com
www.axsome.com

Media:
Darren Opland
Director, Corporate Communications
Axsome Therapeutics, Inc.
One World Trade Center, 22nd Floor
New York, NY 10007
Tel: 929-837-1065
Email: dopland@axsome.com
www.axsome.com

Source: Axsome Therapeutics, Inc.