Axsome Therapeutics Announces AXS-12 Achieves Primary Endpoint in ENCORE Long-Term Phase 3 Trial in Narcolepsy

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AXS-12 statistically significantly reduced the frequency of cataplexy attacks compared to placebo (p=0.017, primary endpoint)

Statistically significant improvement in cognition compared to placebo (p=0.011, NSAQ)

Statistically significant improvement in narcolepsy overall compared to placebo (p=0.024, PGI-C)

Cataplexy response (≥50% improvement) achieved by 72% of patients at 1 month and 82% at 6 months

Improvement in excessive daytime sleepiness (EDS), assessed by the CGI-C, achieved by 84% of patients at 1 month and 78% at 6 months

Improvement in narcolepsy overall, assessed by the CGI-C, achieved by 90% of patients at 1 month and 90% at 6 months

Well-tolerated with long-term safety profile consistent with previously completed trials and no new safety signals detected

NEW YORK, Nov. 26, 2024 (GLOBE NEWSWIRE) -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company developing and delivering innovative 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 in the ENCORE Phase 3 trial, demonstrating a statistically significant improvement in the frequency of cataplexy attacks compared to placebo. AXS-12 was also well tolerated with long-term dosing with a safety profile consistent with that observed in previously completed trials. ENCORE was a multi-center, two-period Phase 3 trial evaluating the long-term efficacy and safety of AXS-12 in patients with narcolepsy with cataplexy, consisting of a 6-month open-label AXS-12 treatment period, followed by a 3-week double-blind, placebo-controlled, randomized withdrawal period. The trial enrolled 68 patients in the 6-month AXS-12 treatment period. Patients (n=42) were then randomized in a 1:1 ratio to continue treatment with AXS-12 or to discontinue AXS-12 and switch to placebo for 3 weeks.

AXS-12 met the primary endpoint of the change from randomization in the frequency of cataplexy attacks as compared to placebo at week 3 of the double-blind period. Patients randomized to switch to placebo experienced a statistically significant worsening in the average weekly number of cataplexy attacks compared with patients randomized to continue AXS-12 treatment, with an increase of 10.29 attacks per week with placebo versus 1.32 with AXS-12, at 3 weeks (p=0.017).

“Clinical evidence continues to support AXS-12 as a novel treatment option for narcolepsy that has the potential to rapidly and durably ameliorate one of the most debilitating symptoms for patients, cataplexy, while also reducing the severity of excessive daytime sleepiness, and improving cognition and overall function,” 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. “Narcolepsy is a complex and heterogeneous condition defined by distinct symptom clusters and there remains great need for options that can address this variety in disease presentation. The results from the ENCORE study support AXS-12 as a potentially important new option for physicians and patients.”

AXS-12 resulted in statistically significant benefit in cognition compared to placebo, as assessed by the Narcolepsy Symptom Assessment Questionnaire (NSAQ) and the Patient Global Impression of Change (PGI-C). A significantly greater proportion of patients randomized to switch to placebo experienced worsening on the NSAQ Ability to Concentrate item compared to those continuing on AXS-12 (52.6% versus 14.3%) at 3 weeks (p=0.011). A significantly greater proportion of patients randomized to switch to placebo also reported worsening in their ability to concentrate, as assessed by the PGI-C, compared to those continuing on AXS-12 (57.9% versus 22.2%) at 3 weeks (p=0.029).

AXS-12 resulted in statistically significant benefit in narcolepsy overall compared to placebo, as assessed by the PGI-C. A significantly greater proportion of patients randomized to switch to placebo reported worsening of their narcolepsy, as assessed by the PGI-C, compared to those continuing on AXS-12 (52.6% versus 16.7%) at 3 weeks (p=0.024).

“The results of the ENCORE trial confirm the efficacy of AXS-12 in patients with narcolepsy with cataplexy, which has now been demonstrated in three positive controlled trials, and indicate that the potential benefits of AXS-12 are substantial and sustained with long-term treatment,” said Dr. Herriot Tabuteau, CEO of Axsome Therapeutics. “We are pleased by the improvements not only in cataplexy, but also in excessive daytime sleepiness and cognition reported by a majority of patients in the trial with long-term AXS-12 treatment. Importantly, these improvements were accompanied by a favorable long-term safety and tolerability profile. We plan to move expeditiously towards an NDA filing for AXS-12 and intend to request a pre-NDA meeting with the FDA.”

During the long-term open-label treatment portion of the trial, patients experienced substantial and sustained improvement of cataplexy with AXS-12 treatment. Patients experienced a 71% reduction from baseline in mean weekly cataplexy attacks at 1 month with AXS-12 treatment, which was sustained with long-term treatment resulting in a 77% reduction at 6 months. Cataplexy response, defined as ≥50% reduction from baseline in weekly

cataplexy attacks, was achieved by 72% of patients at 1 month, and by 82% of patients at 6 months with AXS-12 treatment. Treatment with AXS-12 also substantially increased the percentage of cataplexy-free days (days with zero cataplexy attacks) per week from 14% at baseline to 61% at 1 month and 70% at 6 months.

Long-term open-label treatment with AXS-12 resulted in substantial improvements in excessive daytime sleepiness (EDS), assessed using the Epworth Sleepiness Scale (ESS) and the Clinician Global Impression of Change (CGI-C) scale. Mean ESS scores were reduced by 5.6 points at 1 month, with this improvement maintained with long-term treatment resulting in a mean reduction of 7.3 points at 6 months. Clinicians reported improvement in EDS in a substantial proportion of patients on the CGI-C scale, with 84% of patients achieving EDS improvement at 1 month and 78% of patients at 6 months with AXS-12 treatment.

A substantial proportion of patients reported improvement in cognition with AXS-12 which was sustained with long-term open-label treatment. Improvement in cognition, assessed by the NSAQ Ability to Concentrate item, was reported by 55% of patients at 1 month and 59% at 6 months with AXS-12 treatment. Change in the ability to concentrate was also assessed using the PGI-C scale. The proportion of patients reporting improvement in the ability to concentrate on the PGI-C was 67% at 1 month and 70% at 6 months with AXS-12 treatment.

Long-term open-label treatment with AXS-12 was also associated with improvement in overall narcolepsy status and patient functioning, assessed using the CGI-C, the PGI-C, and the Work Productivity and Activity Impairment Questionnaire (WPAI). On the CGI-C, clinicians reported overall improvement in narcolepsy in 90% of patients at 1 month and also 90% of patients at 6 months with AXS-12 treatment. Results were similar with the patient-reported PGI-C. Impairment due to narcolepsy while working was assessed after treatment with AXS-12 using the WPAI. The percentage of time impaired while working decreased substantially with AXS-12 treatment from 53% at baseline to 34% at 1 month and 24% at 6 months.

AXS-12 was well tolerated with long-term dosing. The safety profile with long-term dosing was consistent with prior trials of AXS-12 with no new safety signals identified. During the 6-month open-label treatment period, the most common adverse events (≥5%) were nausea (5.9%) and tachycardia (5.9%). Over the 6-month treatment period, 17.6% of patients discontinued due to adverse events, with no individual adverse event leading to discontinuation by more than 1 patient. Treatment-related adverse events during the double-blind period were reported in 4.5% of patients in the AXS-12 group and 15% of patients in the placebo group. Rates of discontinuation due to adverse events in the double-blind period were 0% and 5% in the AXS-12 and placebo groups, respectively.

AXS-12 has been granted Orphan Drug Designation for the treatment of narcolepsy. 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.

Double-Blind Efficacy Highlights

- A total of 42 patients were randomized, 22 to continued treatment with AXS-12, and 20 switched to placebo. The primary endpoint was the change from randomization to week 3 in the weekly frequency of cataplexy attacks.
- The primary endpoint was achieved with patients randomized to switch to placebo experiencing a mean increase of 10.29 cataplexy attacks per week compared to a mean increase of 1.32 attacks per week for patients randomized to continue AXS-12 treatment, at 3 weeks (p=0.017).
- A significantly greater proportion of patients randomized to switch to placebo experienced worsening on the NSAQ Ability to Concentrate item compared to those continuing on AXS-12 (52.6% versus 14.3%) at 3 weeks (p=0.011).
- A significantly greater proportion of patients randomized to switch to placebo also reported worsening in their ability to concentrate, as assessed by the PGI-C, compared to those continuing on AXS-12 (57.9% versus 22.2%) at 3 weeks (p=0.029).
- A significantly greater proportion of patients randomized to switch to placebo reported worsening of their narcolepsy overall, as assessed by the PGI-C, compared to those continuing on AXS-12 (52.6% versus 16.7%) at 3 weeks (p=0.024).

Long-Term Efficacy Highlights

A total of 68 patients were treated with AXS-12 for up to 6 months in an open-label fashion. At baseline, the mean number of weekly cataplexy attacks was 31.3 and the mean ESS was 18. Efficacy results for this treatment period are summarized below:

Cataplexy

- Treatment with AXS-12 resulted in a mean reduction from baseline of 22.3 cataplexy attacks per week at 1 month, corresponding to a decrease of 71%. The improvement in cataplexy was maintained with long-term AXS-12 treatment, resulting in a mean reduction of 24.1 cataplexy attacks per week at 6 months, corresponding to a decrease of 77%.
- Cataplexy response, defined as ≥50% reduction from baseline in the weekly frequency of cataplexy attacks, was achieved by 72% of patients at 1 month, and by 82% of patients at 6 months with AXS-12 treatment.
- AXS-12 increased the percentage of cataplexy free days (days with zero cataplexy attacks) per week from 14.3% at baseline to 61% at 1 month and 70% at 6 months.

Excessive Daytime Sleepiness (EDS)

- Treatment with AXS-12 resulted in mean reductions from baseline in the ESS score of 5.6 points at 1 month and 7.3 points at 6 months.
- EDS, assessed by the Clinician Global Impression of Change (CGI-C), was improved in 84% of patients at 1 month, and in 78% of patients at 6 months with AXS-12 treatment.

Cognition

- AXS-12 treatment was associated with an improvement in cognition, assessed by the NSAQ Ability to Concentrate item, with 55% of patients reporting improvement at 1 month, and 59% reporting improvement at 6 months.
- AXS-12 treatment was also associated with an improvement in the ability to concentrate, assessed by the PGI-C, with 67% of patients reporting improvement at 1 month, and 70% reporting improvement at 6 months.

Narcolepsy Overall, Work Productivity

- Narcolepsy overall, assessed by the CGI-C, was improved in 90% of patients at 1 month and 90% at 6 months with AXS-12 treatment.
- AXS-12 treatment was associated with an improvement in narcolepsy overall, assessed by the PGI-C, with 78% of patients reporting improvement at 1 month, and 80% reporting improvement at 6 months.
- AXS-12 treatment was associated with improved patient function by substantially decreasing the time impaired due to narcolepsy while working, assessed by the WPAI, from 53% at baseline to 34% at 1 month and 24% at 6 months.

Long-Term Safety and Tolerability Highlights

Safety results are for all patients enrolled in the ENCORE trial (n=68). Safety results for the 6-month treatment and double-blind periods are summarized below.

- AXS-12 was well tolerated with a safety profile that was consistent with what was previously observed in completed, short-term controlled trials, with no new safety signals detected.
- The most commonly reported adverse events (≥5%) were nausea (5.9%) and tachycardia (5.9%).
- Discontinuations due to adverse events occurred in 17.6% of patients, with no individual event leading to discontinuation by more than 1 patient.
- During the double-blind period, the rates of treatment-related adverse events were 4.5% in the AXS-12 group and 15.0% in the placebo group. Discontinuations due to adverse events in the double-blind period occurred in no patients in the AXS-12 group and in 1 patient in the placebo group.

About the ENCORE Study

ENCORE (Evaluating Continued Treatment with Reboxetine) was a multicenter Phase 3 trial consisting of a 24-week open-label period followed by a 3-week, double-blind, randomized withdrawal period to evaluate the efficacy and long-term safety of AXS-12 in patients with narcolepsy. A total of 68 patients, who rolled over from the SYMPHONY Phase 3 trial of AXS-12, were enrolled into the open-label period and treated with AXS-12 (5 mg) once-daily for the first week, followed by twice daily dosing for the next 23 weeks. Patients who completed the open-label treatment period (n=42) were then randomized in a 1:1 ratio to continue on AXS-12 (n=22) or to switch to placebo (n=20). The mean number of cataplexy attacks at baseline was 31.3. The mean number of cataplexy attacks at randomization was 4.2 (AXS-12) and 6.9 (placebo). The prespecified primary efficacy endpoint was the change in frequency of weekly cataplexy attacks from baseline at randomization to week 3 of the double-blind period. 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.[1-3] 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.[4-5] Narcolepsy is a life-long condition that 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.[6-8]

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

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; 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.