Axsome Therapeutics Announces SYMBRAVO® (meloxicam and rizatriptan) Achieves Primary Endpoint in the EMERGE Phase 3 Trial in Migraine Patients Experiencing Inadequate Response to Oral CGRP Inhibitors

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SYMBRAVO demonstrated statistically significantly greater migraine treatment response compared to prior treatment with an oral CGRP inhibitor (p<0.001, mTOQ-4 total score, primary endpoint)

2-hour pain freedom for most attacks reported at least half the time by 47.9% of patients after SYMBRAVO versus 1.0% after oral CGRPs (p<0.001)

24-hour or greater sustained pain relief after a single dose reported by 47.9% of patients after SYMBRAVO versus 16.7% after oral CGRPs (p<0.001)

Ability to quickly return to normal activities reported by 51.0% of patients after SYMBRAVO versus 11.5% after oral CGRPs (p<0.001)

SYMBRAVO improved quality of life compared to after oral CGRPs (p<0.001, MSQ)

NEW YORK, Feb. 24, 2025 (GLOBE NEWSWIRE) -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company leading a new era in the treatment of central nervous system (CNS) disorders, today announced that the EMERGE Phase 3 trial of SYMBRAVO® (MoSEIC™ meloxicam and rizatriptan) in patients experiencing inadequate response to oral CGRP inhibitors met its primary endpoint, with SYMBRAVO demonstrating statistically significantly greater migraine treatment response compared to oral CGRP inhibitors, as measured by the Migraine Treatment Optimization Questionnaire (mTOQ-4). SYMBRAVO is a novel multi-mechanistic approach to treating migraine that targets multiple pathways underlying a migraine attack. In the trial, SYMBRAVO rapidly and substantially improved migraine pain and most bothersome symptoms.

EMERGE was an open-label trial that enrolled migraine patients who were undergoing treatment with an oral CGRP inhibitor for at least one month and experiencing an inadequate response to the oral CGRP inhibitor, with treatment response assessed using the mTOQ-4. Enrolled patients were switched to treatment with SYMBRAVO for their next four attacks. Treatment responses after the oral CGRP inhibitor treatment period and after the SYMBRAVO treatment period were compared. A total of 96 patients were enrolled and 365 migraine attacks were treated with SYMBRAVO in the trial.

EMERGE met the primary endpoint by demonstrating statistically significantly greater migraine treatment response with SYMBRAVO compared to treatment response with prior oral CGRP inhibitors, as assessed by the mTOQ-4 total score (5.2 versus 2.8, p<0.001). Statistically significantly greater proportions of patients achieved clinical response on the 2-hour pain freedom, sustained pain freedom, ability to return to normal activities, and ability to plan daily activities mTOQ-4 items with SYMBRAVO compared to oral CGRP inhibitors:

- Pain freedom within 2 hours for most attacks was reported half the time or more by 47.9% of patients after treatment with SYMBRAVO, compared to 1.0% of patients after treatment with oral CGRPs (p<0.001).
- Sustained relief of migraine pain for at least 24 hours following a single dose of medication was reported half the time or more by 47.9% of patients after treatment with SYMBRAVO, compared to 16.7% of patients after treatment with oral CGRPs (p<0.001).
- The ability to quickly return to normal activities after taking their medication was reported half the time or more by 51.0% of patients after treatment with SYMBRAVO, compared to 11.5% of patients after treatment with oral CGRPs (p<0.001).
- The proportion of patients who reported being comfortable enough with their medication to be able to plan daily activities half the time or more was 63.5% after treatment with SYMBRAVO, compared to 26.0% after treatment with oral CGRPs (p<0.001).

Further, SYMBRAVO treatment resulted in a statistically significant improvement in overall quality of life and daily functioning, as assessed by all three domains of the Migraine-Specific Quality of Life Questionnaire (MSQ), compared to after treatment with oral CGRP inhibitors (p=0.003 to <0.001).

Richard B. Lipton, MD, Professor of Neurology and Director of the Montefiore Headache Center, Albert Einstein College of Medicine, commented, “The results of the EMERGE study demonstrate significant improvements in migraine treatment response with SYMBRAVO for patients previously experiencing inadequate response to oral CGRPs based on the mTOQ-4. Migraine is a disabling neurological condition, and the multiple mechanisms of action of SYMBRAVO may be relevant to the complex and heterogenous nature of this serious condition. These data from the EMERGE study are compelling and provide further evidence for the utility of SYMBRAVO across a variety of migraine settings.”

In this population of patients with a prior inadequate response to an oral CGRP inhibitor, SYMBRAVO rapidly and substantially relieved migraine pain

within 2 hours, with benefits sustained through 24 and 48 hours after a single dose. Across all treated attacks, pain relief 2 hours after dosing with SYMBRAVO was achieved by 50.0% of patients, with some patients experiencing pain relief as early as 30 minutes after dosing. The pain relief achieved 2 hours after dosing was sustained through 24 and 48 hours by 78% and 75% of patients respectively. Pain freedom and freedom from the most bothersome symptom 2 hours after dosing with SYMBRAVO was achieved by 22.5% and 26.6% of patients, respectively.

Overall improvement of migraine, measured using the Patient Global Impression of Change (PGI-C), was experienced early and in a substantial proportion of patients after treatment with SYMBRAVO. Overall improvement of their migraine was reported by 26.0% of patients 30 minutes post dose, and by 69.2% of patients 2 hours post dose.

SYMBRAVO was well tolerated with a safety profile that was consistent with what has been previously observed in prior studies. The most commonly reported adverse events (≥2%) were fatigue (3.1%), nausea (3.1%), vomiting (2.1%), muscle tightness (2.1%), and dizziness (2.1%).

Herriot Tabuteau, MD, Chief Executive Officer of Axsome Therapeutics, said, “We’re pleased to share the results of the Phase 3 EMERGE trial, which further underscore the robust efficacy of SYMBRAVO and its potential to effectively treat migraine attacks across a range of patient populations with varying pain intensities and prior responses to acute treatments. We look forward to launching SYMBRAVO in the U.S. in the coming months and offering a new treatment option that could make a meaningful difference for patients suffering from this disabling condition.”

About the EMERGE Trial

EMERGE (Evaluating Outcomes of AXS-07 after Acute Gepant Failures) was a Phase 3, open-label, multicenter trial to evaluate the efficacy and safety of SYMBRAVO in the acute treatment of migraine in patients experiencing inadequate response to an oral calcitonin gene-related peptide (CGRP) inhibitor. Eligible patients must have been using an oral CGRP inhibitor for the acute treatment of migraine for at least 1 month prior to enrollment (having treated at least 4 migraines with an oral CGRP inhibitor) and have had an inadequate response to the oral CGRP inhibitor. An inadequate response was defined as a score of ≤7 on the Migraine Treatment Optimization Questionnaire (mTOQ-4), including a score of 1 (“less than half the time”) or 0 (“rarely” or “never”) on Question 2 (achievement of pain freedom 2 hours after taking migraine medication). Enrolled patients were switched from their oral CGRP inhibitor to SYMBRAVO and treated the next 4 migraine attacks with SYMBRAVO over a period of up to 8 weeks. A total of 96 patients were enrolled in the trial. The primary efficacy endpoint to assess treatment response with SYMBRAVO versus oral CGRP inhibitors was the change in the mTOQ-4 total score from the oral CGRP inhibitor treatment period to the SYMBRAVO treatment period.

About the Migraine Treatment Optimization Questionnaire (mTOQ-4)

The mTOQ-4 is a validated questionnaire that assesses the adequacy of migraine treatment efficacy based on four aspects of response to acute treatment: 2-hour pain freedom; sustained pain freedom; ability to quickly return to daily activities; and comfort planning daily activities. Each of the 4 items is scored, using frequency-based options, as never [0], rarely [0], less than half the time [1], and half of the time or more [2]. Total scores range from 0 to 8 with higher total scores corresponding to greater treatment optimization. A total score of 8 corresponds to maximum treatment efficacy, with total scores of 4-7 corresponding to moderate, 1-3 to poor, and 0 to very poor treatment optimization.[1]

About Migraine

Migraine is a serious neurological condition characterized by recurrent attacks of pulsating, often severe and disabling head pain associated with nausea, sensitivity to light, and sensitivity to sound.[2] It is estimated that over 39 million Americans suffer from migraine, and it is the leading cause of disability among neurological disorders in the United States according to the American Migraine Foundation.[3-5] Extensive surveys of migraine sufferers underscore the unmet need for therapies that work faster, more consistently, and result in less symptom recurrence.[6,7] Over 70% of patients report experiencing an inadequate response to their oral, acute migraine treatment.[8]

About SYMBRAVO

SYMBRAVO is a novel, oral, single-dose medicine approved for the acute treatment of migraine with or without aura in adults. SYMBRAVO consists of MoSEIC™ meloxicam and rizatriptan. Meloxicam is a new molecular entity for migraine enabled by Axsome’s MoSEIC (Molecular Solubility Enhanced Inclusion Complex) technology, which enables the rapid absorption of meloxicam while maintaining a long plasma half-life. Meloxicam is a COX-2 preferential non-steroidal anti-inflammatory drug (NSAID) and rizatriptan is a 5-$HT_{1B/1D}$ agonist. SYMBRAVO is designed to provide rapid, enhanced, and consistent migraine pain relief, and reduced symptom recurrence. The exact mechanism of action of SYMBRAVO in the treatment of acute migraine is unknown.

For more information, visit www.symbravo.com.

What is SYMBRAVO (sim-BRAH-voh)? SYMBRAVO is a combination of meloxicam (an NSAID) and rizatriptan (a triptan). SYMBRAVO is an oral prescription medicine used to treat acute migraine headaches with or without aura in adults.

SYMBRAVO is not used to prevent or decrease the number of migraine headaches you have or for treatment of hemiplegic or basilar migraines. SYMBRAVO is not indicated as a treatment for cluster headaches or for use in children.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT SYMBRAVO?

SYMBRAVO may increase the risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase with increasing doses, and longer use, of NSAIDs.

Do not take SYMBRAVO right before or after a heart surgery called a “coronary artery bypass graft” (CABG).

Avoid taking SYMBRAVO after a recent heart attack unless your healthcare provider (HCP) tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

Stop taking SYMBRAVO and get emergency help right away if you have any of the following symptoms which can be indicative of a heart attack or stroke:

- discomfort in your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded
- weakness in one part or one side of your body
- slurred speech

People with risk factors for heart disease should not take SYMBRAVO unless a heart exam is done and shows no problem. You have higher risk for heart disease if you:

- have high blood pressure
- have high cholesterol
- smoke
- are overweight
- have diabetes or a family history of diabetes

SYMBRAVO can increase the risk of potentially life-threatening bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach, and intestines that can occur anytime during use and without warning symptoms.

SYMBRAVO may cause serious allergic or skin reactions which can be life-threatening. Stop taking SYMBRAVO and get emergency help right away if you develop:

- sudden wheezing or problems breathing or swallowing
- rash or reddening of your skin with blisters or peeling
- blisters or bleeding of your lips, eye lids, mouth, nose, or genitals
- swelling of your lips, tongue, throat or body
- fainting

SYMBRAVO already contains an NSAID (meloxicam). Do not use SYMBRAVO with other medicines to lessen pain or fever or with other medicines for colds or sleeping problems without talking to your HCP first, because they may contain an NSAID also.

Do not take SYMBRAVO if you:

- have or had heart problems or right before or after heart bypass surgery
- have or had a stroke or transient ischemic attack (TIA)
- have or had blood vessel problems of your legs and arms, stomach (ischemic bowel disease), or kidneys
- have or had hemiplegic or basilar migraines
- have uncontrolled high blood pressure
- take propranolol containing medicines
- have taken other triptan or ergot-containing medicines within the last 24 hours
- take an antidepressant medicine called monoamine oxidase inhibitor (MAOI) or have taken a MAOI within the last 2 weeks
- are allergic to meloxicam, rizatriptan, NSAIDs, or any of the ingredients in SYMBRAVO
- have had an asthma attack, hives, or other allergic reaction after taking aspirin or any other NSAIDs
- have moderate to severe kidney problems and are at risk of kidney failure or if you are on dialysis

SYMBRAVO may cause serious side effects. These serious side effects include:

- heartbeats that are too fast or too slow (arrhythmias)
- new or worse high blood pressure

- heart failure
- life-threatening skin reactions
- liver or kidney problems including organ failure
- low red blood cell count (anemia)
- asthma attacks in people who have asthma

Medication Overuse Headaches: Some people who use too many SYMBRAVO tablets may have worse headaches. If your headaches get worse, your HCP may decide to stop your treatment with SYMBRAVO.

Stop taking SYMBRAVO and get emergency help right away if you have any of the following:

- **Stomach and intestinal problems.** Symptoms of gastrointestinal and colonic ischemic events may include sudden or severe stomach pains even after meals; sudden weight loss; severe nausea, vomiting, constipation, diarrhea; and bloody diarrhea.
- **Circulation problems to legs and feet.** Symptoms of peripheral vascular ischemia may include cramping and pain in your legs and hips; heaviness or tightness in leg muscles; burning, aching, numbness, tingling, or weakness in your legs, feet, or toes; cold feelings or color changes in one or both legs or feet.
- **Serotonin syndrome.** Can happen when taking SYMBRAVO with antidepressant medicines called SSRIs or SNRIs. Stop taking SYMBRAVO and call your doctor right away if you have any of the following symptoms:
    - mental status changes including agitation, hallucinations, or coma
    - fast heartbeat
    - changes in your blood pressure
    - increased body temperature
    - tight muscles
    - trouble walking

Stop taking SYMBRAVO and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- vomiting blood
- more tired or weaker than usual
- blood in your bowel movement or it is black and sticky like tar
- diarrhea
- itching, skin rash, or blisters with fever
- unusual weight gain
- your skin or eyes look yellow
- indigestion or stomach pain
- swelling of the arms, legs, hands, or feet
- flu-like symptoms

- tenderness in your right upper side
- vision problems

COMMON SIDE EFFECTS

The most common side effects of SYMBRAVO include dizziness and tiredness.

These are not all the possible side effects of SYMBRAVO. Tell your doctor if you have any side effects. You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1–800-FDA-1088.

BEFORE USING

- **Tell your HCP about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.**
- **It is important to tell your HCP if you are taking:**
    - Propranolol containing medicines such as Inderal® LA or Innopran® XL
    - Aspirin or other anti-coagulants (blood thinners)
    - Medicines to help your mood including SSRIs and SNRIs
- If you are unsure if you take any of these medicines, ask your HCP. They can tell you if it is safe to take SYMBRAVO with your other medicines.
- Tell your HCP if you are pregnant or plan to become pregnant. SYMBRAVO is not recommended during pregnancy. Taking NSAIDs, including SYMBRAVO, at about 20 weeks of pregnancy or later may harm your unborn baby. **NSAIDs, including SYMBRAVO, should not be taken after about 30 weeks of pregnancy.**
- Tell your HCP if you are breastfeeding or plan to breastfeed.

Tell your HCP about all your medical conditions, including if you:

- have or have had heart problems, high blood pressure, chest pain, or shortness of breath
- have any risk factors for heart or blood vessel problems
- have kidney or liver problems
- have asthma

Review the list below with your HCP. SYMBRAVO may not be right for you if:

- take daily preventative aspirin
- you are pregnant or plan to become pregnant
- you are breastfeeding or plan to breastfeed

HOW TO TAKE

- SYMBRAVO is available by prescription only.
- Take SYMBRAVO exactly as instructed by your HCP.
- The maximum daily dose of SYMBRAVO is 1 tablet. Talk to your HCP about what to do if your headache does not go away or comes back.
- Take SYMBRAVO for the shortest time needed.
- Swallow SYMBRAVO tablets whole. **Do not** crush, chew, or divide the tablets.

- SYMBRAVO can be taken with or without food.
- Do not give SYMBRAVO to other people.
- If you take too much SYMBRAVO call your poison control center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

LEARN MORE

For more information about SYMBRAVO, call 866-496-2976 or visit SYMBRAVO.com.

This summary provides basic information about SYMBRAVO but does not include all information known about this medicine. Read the information that comes with your prescription each time your prescription is filled. This information does not take the place of talking with your doctor. Be sure to talk to your doctor or other HCP about SYMBRAVO and how to take it. Your HCP is the best person to help you decide if SYMBRAVO is right for you.

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Please see full Prescribing Information, including Boxed Warning for risk of serious cardiovascular and gastrointestinal adverse events, and Medication Guide.

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, excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea, and migraine, 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 commercial success of the Company's Sunosi®, Auvelity®, and Symbravo® 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; 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 commercialization of Sunosi, Auvelity, and Symbravo 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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