Axsome Therapeutics to Focus on Growing Core CNS Portfolio; Establishes Axsome Pain and Primary Care Business Unit to Enhance Value of Non-CNS Assets

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Axsome PPC to include three novel, non-opioid, Phase 3-stage product candidates for chronic pain

145 issued Axsome PPC patents, including 21 covering neridronate, provide protection as far as 2036

Indications include osteoarthritis, osteoporosis, and complex regional pain syndrome

NEW YORK, Oct. 11, 2018 (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 it will focus on its growing core CNS portfolio. As a result, the Company has created Axsome Pain and Primary Care (Axsome PPC), a new business unit to house, manage, develop and enhance the value of Axsome's non-CNS assets. The assets in Axsome PPC include the Company's pain and primary care product candidates and related intellectual property.

"The new corporate structure allows us to maintain focus on Axsome's growing core CNS portfolio, and to position the non-CNS assets for continued clinical development and enhanced value creation by placing them in a discrete business unit," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "The differentiated product candidates and technology in Axsome PPC have the potential to significantly benefit patients living with pain and other serious conditions including osteoporosis. The new structure provides for clearer communication of the potential of these assets and facilitates business development activities related to them."

Core CNS Portfolio

Axsome's core CNS portfolio currently includes three differentiated, clinical-stage product candidates:

- **AXS-05**: AXS-05 is a novel, oral, investigational medicine consisting of dextromethorphan (an NMDA receptor antagonist, sigma-1 receptor agonist, and serotonin and norepinephrine reuptake inhibitor) and bupropion (a norepinephrine and dopamine reuptake inhibitor, which also increases the bioavailability of dextromethorphan). AXS-05 is currently in a Phase 3 trial in treatment resistant depression (TRD), a Phase 2/3 trial in agitation associated with Alzheimer's disease (AD), a Phase 2 trial in Major Depressive Disorder (MDD), and a Phase 2 trial in smoking cessation. AXS-05 has been granted U.S. Food and Drug Administration (FDA) Fast Track designations for the treatment of TRD and for the treatment of AD agitation.

- **AXS-07**: AXS-07 is a novel, oral, rapidly absorbed, investigational medicine consisting of MoSEIC™ meloxicam and rizatriptan. AXS-07 utilizes Axsome's proprietary MoSEIC™ (Molecular Solubility Enhanced Inclusion Complex) technology to substantially increase the solubility and speed the absorption of meloxicam while maintaining durability of action. Axsome anticipates initiating a Phase 3 trial of AXS-07 for the acute treatment of migraine in the fourth quarter of 2018.

- **AXS-09**: AXS-09 is a novel, oral medicine consisting of chirally pure esbupropion and dextromethorphan. Axsome plans to evaluate AXS-09 in future CNS indications.

Axsome PPC Portfolio

The assets in Axsome PPC include three Phase 3-stage product candidates. Two of the product candidates (AXS-06 and AXS-02) are being developed directly by Axsome, and one of the candidates (neridronate) is covered by Axsome's intellectual property portfolio. These product candidates are being developed for five different indications including the signs and symptoms of osteoarthritis and rheumatoid arthritis, osteoporosis, the pain of knee osteoarthritis, chronic low back pain, and complex regional pain syndrome:

- **AXS-06**: AXS-06 is a Phase 3-ready, oral, non-opioid, rapidly absorbed, once-daily, investigational medicine, consisting of MoSEIC™ meloxicam and esomeprazole, which is being developed for the treatment of chronic pain. Meloxicam is a long-acting nonsteroidal anti-inflammatory drug (NSAID) with COX-2 preferential inhibition and potent pain-relieving efficacy. AXS-06 utilizes Axsome's proprietary MoSEIC™ technology to substantially increase the solubility and speed the absorption of meloxicam while maintaining durability of action. Results of a Phase 1 trial indicate that orally administered AXS-06 provides absorption of meloxicam that is more rapid than that reported with intramuscular administration,

highlighting the potential for faster and more convenient pain relief. The esomeprazole component of AXS-06 has been shown to reduce the occurrence of NSAID-induced gastrointestinal ulcers providing the potential for enhanced gastrointestinal safety. The potential efficacy and safety advantages of AXS-06 as compared to currently available NSAIDs could provide significant benefits to patients.

Axsome received Pre-IND written guidance from the FDA on a proposed clinical developmental program for AXS-06 for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and the reduction in the risk of developing upper gastrointestinal ulcers in patients at risk for developing NSAID-associated upper gastrointestinal ulcers. Based on this guidance, Axsome believes that AXS-06 is Phase 3-ready.

In September 2018, Axsome presented at the International Association for the Study of Pain (IASP) 2018 World Congress on Pain in Boston, Massachusetts, previously announced positive topline results from a Phase 1 pharmacokinetic trial of AXS-06. The study compared the pharmacokinetics of meloxicam and esomeprazole after oral administration of AXS-06 tablets (MoSEIC meloxicam 15 mg, esomeprazole 40 mg), and commercially available Mobic® tablets (15 mg meloxicam) and Nexium® capsules (40 mg esomeprazole) in healthy volunteers. The median time to reach the maximum plasma concentration of meloxicam, the trial's primary endpoint, was 9 times faster for AXS-06 as compared to Mobic (0.5 hour versus 4.5 hours for AXS-06 and Mobic®, respectively, $p<0.0001$). AXS-06 also demonstrated higher mean maximum plasma concentration ($p=0.0018$), faster time to therapeutic plasma concentration ($p<0.0001$), and time to half-maximum plasma concentration ($p<0.0001$) as compared to Mobic. Terminal half-lives for meloxicam were similar for AXS-06 and Mobic. Plasma concentrations and terminal half-lives of esomeprazole after AXS-06 and Nexium® administration were comparable.

- **AXS-02**: AXS-02 (disodium zoledronate tetrahydrate) is a potent, orally administered, osteoclast inhibitor. It is being developed as an oral, very long-acting treatment for osteoporosis; and as an oral, non-opioid, targeted, potentially first-in-class therapeutic for chronic pain. AXS-02 has a high affinity for bone mineral that results in therapeutic effects lasting potentially as long as one year after a single course of treatment.

  Osteoporosis: The potential for AXS-02 in the treatment of osteoporosis is currently being evaluated in a Phase 2 trial examining the ability of orally administered AXS-02 to reduce bone resorption over a 12-month period following a single 6-week treatment course (one tablet a week for 6 weeks). Zoledronic acid, the active ingredient in AXS-02, is currently approved for the treatment of osteoporosis but is currently available only as an intravenous formulation. In contrast, AXS-02 is a novel oral formulation that has resulted in rapid absorption of zoledronic acid. The ongoing Phase 2 trial enrolled patients with complex regional pain syndrome who had been treated in the CREATE-1 trial. As previously reported, in that study, AXS-02 treatment resulted in a significant reduction of serum CTx, considered the reference standard marker of bone resorption by the International Osteoporosis Foundation, as compared to placebo ($p<0.0001$) three months after a single treatment course. The current Phase 2 trial is examining the durability of this effect up to one year after treatment.

  Osteoporosis is a degenerative bone condition characterized by an imbalance in bone resorption and formation resulting in porous and brittle bones that are prone to fracture. Increased bone turnover markers, especially serum CTx, are associated with a higher incidence of osteoporosis and fracture risk. An estimated 200 million women are affected worldwide by osteoporosis, resulting in over 8.9 million fractures annually. Osteoporotic fractures occur in 1 in 3 women over age 50 and in 1 in 5 men over age 50. In 2017, worldwide sales of branded osteoporosis drugs totaled over $7.3 billion.

  Knee OA associated with BMLs: AXS-02 is being evaluated in the COAST-1 Phase 3 trial for the treatment of the pain of knee osteoarthritis (OA) associated with bone marrow lesions (BMLs). An independent data monitoring committee (IDMC) conducted an interim analysis of the COAST-1 trial and recommended that it be continued to full enrollment. Screening in the trial was paused prior to the interim analysis and is anticipated to resume after the final readout from the ongoing Phase 3 trial of Axsome's AXS-05 product candidate for treatment resistant depression, as previously disclosed. AXS-02 has been granted U.S. Food and Drug Administration (FDA) Fast Track designation for the treatment of knee OA associated with BMLs.

  CLBP associated with MCs: Axsome received IND clearance from the FDA to proceed with a Phase 3 trial to evaluate AXS-02 in the treatment of chronic low back pain (CLBP) associated with Modic changes (MCs).

- **Neridronate**: Neridronate (neridronic acid) is a Phase 3-stage, intravenously administered bisphosphonate compound whose use for the treatment of certain pain conditions, including complex regional pain syndrome (CRPS), is covered by 20 issued and 1 allowed Axsome patents which provide protection out to 2033. CRPS is a debilitating condition characterized by severe, continuous, burning or throbbing pain in a limb. It is considered to be one of the most painful

conditions, results in loss of physical function, and can lead to significant and sometimes permanent disability. Axsome's extensive CRPS intellectual property portfolio reflects Axsome's early and continued efforts and commitment to develop an effective treatment for this debilitating condition for which there is currently no approved drug.

Neridronate is currently being studied in two pivotal Phase 3 trials for the treatment of complex regional pain syndrome (CRPS) by Grünenthal GmbH (Grünenthal). The Phase 3 trials were announced in June 2018 and are investigating the efficacy and safety of neridronate in 360 patients with CRPS. Grünenthal has recently filed post grant reviews (PGRs) on two of the issued patents covering neridronate for the treatment of CRPS. Neridronate has been granted Breakthrough Therapy, Fast Track, and Orphan Drug designations for the treatment of CRPS by the FDA. The Breakthrough Therapy designation is supported by data from a randomized, double-blind, placebo-controlled Phase 2 clinical trial showing significant reduction in pain and symptoms of CRPS with neridronic acid treatment, according to public disclosures.

Axsome PPC Patent Portfolio

The intellectual property of Axsome PPC includes 145 issued and more than 90 pending patents which provide protection as far as 2036. These patents cover AXS-02, other bisphosphonates and related compounds, and AXS-06. Of the current portfolio, 21 issued or allowed patents cover the use of neridronate for pain, including 10 patents that specifically cover CRPS, providing patent protection out to 2033. Axsome PPC is currently a business unit and not a separate legal entity, and all of the assets are still held by Axsome Therapeutics.

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 CNS product candidate portfolio includes three clinical-stage candidates, AXS-05, AXS-07, and AXS-09. AXS-05 is currently in a Phase 3 trial in treatment resistant depression (TRD), a Phase 2/3 trial in agitation associated with Alzheimer's disease (AD), a Phase 2 trial in Major Depressive Disorder (MDD), and a Phase 2 trial in smoking cessation. AXS-07 is being developed for the acute treatment of migraine. AXS-05, AXS-07, and AXS-09 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 and completion of the trials, futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials; 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 or other regulatory authority approval of, or other action with respect to, our product candidates; 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; 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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