Axsome Therapeutics Announces Primary Endpoint Met in Phase 1 Trial of Next Generation Product Candidate AXS-09 Containing Chirally Pure Esbupropion and Dextromethorphan

February 26, 2018

Chirally pure and stable single enantiomers of bupropion achieved

AXS-09 consists of esbupropion and dextromethorphan for CNS disorders

Esbupropion is the chirally pure S*-enantiomer of bupropion*

AXS-09 results in substantial increases in dextromethorphan plasma levels (p<0.0001)

NEW YORK, Feb. 26, 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 positive topline clinical trial results from a Phase 1 pharmacokinetic study of AXS-09, a novel, oral medicine consisting of esbupropion and dextromethorphan being developed for the treatment of CNS disorders. Esbupropion (*S*-bupropion) is the *S*-enantiomer of bupropion, a dopamine and norepinephrine reuptake inhibitor and nicotinic acetylcholine receptor antagonist which also serves to increase the bioavailability of dextromethorphan. Results of the Phase 1 trial demonstrated that AXS-09 resulted in substantial increases in dextromethorphan plasma concentrations, the trial's primary endpoint, into a potentially therapeutic range with repeated dosing (p<0.0001 day 1 versus day 8). AXS-09 was well tolerated with no serious adverse events reported in the trial.

AXS-09 is enabled by Axsome's technical success at isolating chirally pure and chemically stable single enantiomers of bupropion, and formulating them into dosage forms that maintain their chirality. Enantiomers are molecules which are identical in chemical structure but which differ in the three-dimensional arrangement of the atoms (i.e. mirror images). Based on the results of this Phase 1 trial and preclinical data, Axsome believes that the individual enantiomers of bupropion (*R*-bupropion and *S*-bupropion) may each have unique properties that render them potentially useful in different indications. To Axsome's knowledge, this is the first time that stable, chirally pure single enantiomers of bupropion have been successfully formulated and dosed in a clinical trial.

The increased plasma concentrations of dextromethorphan after dosing with AXS-09, which contains the chirally pure *S*-enantiomer of bupropion, are comparable to those achieved with dosing of the company's first generation product candidate AXS-05 (bupropion and dextromethorphan) which contains racemic bupropion (equal amounts of the *S*- and *R*-enantiomers). Results of this Phase 1 trial coupled with preclinical data also indicate the potential for enhanced absorption and therapeutic effect of the *S*-enantiomer as compared to the *R*-enantiomer.

"We are developing a robust portfolio of novel treatments for CNS disorders, which is an area of high unmet medical needs," said Cedric O'Gorman, M.D., Senior Vice President, Clinical Development and Medical Affairs of Axsome. "We are actively progressing AXS-05 in our ongoing Phase 3 trial in treatment resistant depression and Phase 2/3 trial in agitation in patients with Alzheimer's disease, and we look forward to the results of those trials. Based on the positive Phase 1 results, AXS-09 provides us with another attractive product candidate that merits evaluation in future CNS indications."

"The successful results with AXS-09 reflect Axsome's continued scientific innovation and are additive to AXS-05 which is already in late-stage clinical trials," said Herriot Tabuteau, M.D., Chief Executive Officer of Axsome. "With AXS-05 and AXS-09, we are building a franchise of differentiated medicines targeting both glutamatergic and monoaminergic neurotransmission with potential applicability in numerous CNS disorders."

AXS-09 is yet another product candidate generated using Axsome's proprietary medicinal chemistry and formulation technologies which allow the design of new and innovative medicines to treat CNS conditions. These capabilities, which have yielded five clinical-stage product candidates, include: 1) chiral chemistry and formulation to identify, isolate and stabilize chirally pure enantiomers, 2) metabolic inhibition as a novel drug delivery method to increase the bioavailability and prolong the half-life of target drug molecules, 3) the MoSEIC™ technology which is designed to substantially increase the solubility and speed the absorption of target drug molecules, and 4) proprietary chemical synthesis and analysis to increase the solubility and enable the oral delivery of target drug molecules.

Phase 1 Trial Design

The study was a randomized, multiple-dose, parallel group pharmacokinetic trial. A total of 40 healthy adult subjects were randomly assigned to treatment with AXS-09 (esbupropion and dextromethorphan), *R*-bupropion and dextromethorphan, single-entity *S*-bupropion, or single-entity *R*-bupropion tablets, for 8 days under fasting conditions. Plasma concentrations of dextromethorphan, bupropion, and their metabolites were measured. The primary endpoint was the change in dextromethorphan plasma concentrations from day 1 to day 8.

About AXS-09

AXS-09 is a novel, oral medicine consisting of chirally pure esbupropion and dextromethorphan being developed for the treatment of central nervous system disorders. Esbupropion is the *S*-enantiomer of bupropion, a dopamine and norepinephrine reuptake inhibitor and nicotinic acetylcholine receptor antagonist which also serves to increase the bioavailability of dextromethorphan. Dextromethorphan is an NMDA receptor antagonist,

sigma-1 receptor agonist, an inhibitor of the serotonin and norepinephrine transporters, and a nicotinic acetylcholine receptor antagonist. AXS-09 is an investigational drug product not approved by the FDA.

About AXS-05

AXS-05 is a novel, oral medicine under development for the treatment of central nervous system (CNS) disorders. AXS-05 utilizes Axsome's technology of combining bupropion and dextromethorphan. Dextromethorphan is an NMDA receptor antagonist, sigma-1 receptor agonist, an inhibitor of the serotonin and norepinephrine transporters, and a nicotinic acetylcholine receptor antagonist. Bupropion serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. AXS-05 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 product candidate portfolio includes five clinical-stage candidates, AXS-02, AXS-05, AXS-06, AXS-07, and AXS-09. AXS-05 is currently in a Phase 3 trial in treatment resistant depression (TRD) and a Phase 2/3 trial in agitation in patients with Alzheimer's disease (AD). AXS-05 is also being developed for smoking cessation. AXS-02 is currently in a Phase 3 trial in knee osteoarthritis (OA) associated with bone marrow lesions (BMLs) with an additional Phase 3 trial planned in chronic low back pain (CLBP) associated with Modic changes (MCs). AXS-07 is being developed for the acute treatment of migraine. AXS-06 is being developed for the treatment of osteoarthritis and rheumatoid arthritis and for the reduction of the risk of NSAID-associated gastric ulcers. AXS-02, AXS-05, AXS-06, AXS-07, and AXS-09 are investigational drug products not approved by the FDA. For more information, please visit the company website at www.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.

Axsome Contact:
Mark Jacobson
Senior Vice President, Operations
Axsome Therapeutics, Inc.
25 Broadway, 9th Floor
New York, NY 10004
Tel: 212-332-3243
Email: mjacobson@axsome.com
www.axsome.com

Source: Axsome Therapeutics, Inc.