Axsome Therapeutics Announces Expedited Development and Pivotal Status for AXS-05 in the Treatment of Major Depressive Disorder based on FDA Breakthrough Therapy Meeting

May 6, 2019

Previously completed active-controlled ASCEND trial in MDD now considered as pivotal; sufficient with ongoing STRIDE-1 Phase 3 trial for NDA in MDD

Target randomization for STRIDE-1 Phase 3 trial reached; screening to continue to build required NDA safety database

Initiation of placebo-controlled Phase 3 trial in MDD anticipated in 2Q 2019; provides additional NDA path with ASCEND trial and builds required NDA safety database

Topline results of both STRIDE-1 Phase 3 trial in TRD and planned placebo-controlled Phase 3 trial in MDD expected in 2H 2019

AXS-05 has potential to be first oral NMDA receptor antagonist with multimodal activity for the treatment of depression

Company to host conference call today at 8:00 AM Eastern

NEW YORK, May 06, 2019 (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 the development status and plan for AXS-05 in the treatment of major depressive disorder (MDD) and treatment resistant depression (TRD) have been expedited following a Breakthrough Therapy meeting with the U.S. Food and Drug Administration (FDA). AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.

As part of the expedited development program, the Company's previously completed ASCEND trial in MDD is now considered sufficient with the ongoing STRIDE-1 Phase 3 trial in TRD, if positive, to support the filing of an NDA (New Drug Application) for approval of AXS-05 for the treatment of MDD. Alternatively, Axsome may file an NDA for AXS-05 for the treatment of MDD with the completed ASCEND trial and a placebo-controlled Phase 3 trial of AXS-05 in MDD. Axsome intends to initiate this placebo-controlled Phase 3 MDD trial in the second quarter of 2019.

Target enrollment in the ongoing STRIDE-1 Phase 3 trial has been reached. Based on the now accelerated timeline to NDA filing, patient screening in this trial however will continue in order to build the agreed-upon patient safety database required for an NDA filing. Axsome now expects topline results for both the Phase 3 STRIDE-1 trial in TRD, and the planned placebo-controlled Phase 3 trial in MDD, in the second half of 2019, with an NDA filing anticipated in 2020.

Also, as part of the expedited development program, a TRD indication for AXS-05 can now be supported by a placebo-controlled Phase 3 trial in TRD, in conjunction with the ongoing STRIDE-1 active-controlled trial, if positive, and the completed ASCEND trial.

"Axsome is very pleased with the FDA feedback from our recent Breakthrough Therapy meeting, which provided defined, streamlined NDA paths for AXS-05 in both major depressive disorder and treatment resistant depression," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "The expedited development plan significantly accelerates the potential filing of an NDA, now expected in 2020, for approval of our novel, oral, NMDA receptor antagonist with multimodal activity for the treatment of depression. If successfully developed, AXS-05 would represent a novel antidepressant with one of the first new mechanisms of action in several decades for the treatment of patients with this debilitating condition."

Breakthrough Therapy Meeting Outcomes:

- Completed ASCEND trial in MDD, now considered as pivotal, is sufficient with the ongoing STRIDE-1 trial in TRD, if positive, to support an NDA filing for AXS-05 for the treatment of MDD.
- A placebo-controlled Phase 3 trial in MDD, if positive, in conjunction with the completed ASCEND trial may also support an NDA filing for AXS-05 in the treatment of MDD.
- A safety database of MDD and TRD patients totaling at least 300 patients treated with AXS-05 for at least six months and at least 100 patients treated for one year is required for the NDA filing. Patients completing the ongoing STRIDE-1 and the planned placebo-controlled Phase 3 MDD trials will enter an open-label safety extension trial to build the required safety database.
- A TRD indication may be supported by a placebo-controlled Phase 3 trial in TRD, if positive, in conjunction with the

ongoing STRIDE-1 trial, if positive, and the completed ASCEND trial.

In March 2019, Axsome received Breakthrough Therapy Designation from the FDA for AXS-05 for the treatment of MDD. A Breakthrough Therapy designation is granted to potentially expedite development and review timelines for a promising investigational medicine when preliminary clinical evidence indicates it may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies for a serious or life-threatening condition. The designation for AXS-05 in MDD was supported by the recent positive results from the Phase 2 ASCEND study, a randomized, double-blind, active-controlled, multicenter, U.S. trial, in which 80 patients with confirmed moderate to severe MDD were treated with AXS-05 or the active comparator bupropion. In this trial, treatment with AXS-05 resulted in a substantial, rapid, and statistically significant reduction in depressive symptoms as compared to the active comparator bupropion. On the pre-specified primary endpoint, AXS-05 demonstrated a statistically significant average mean reduction from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score over the 6-week treatment period of 13.7 points for AXS-05 compared to 8.8 for bupropion ($p<0.001$). AXS-05 was safe and well tolerated with the most commonly reported adverse events in the AXS-05 arm being nausea, dizziness, dry mouth, decreased appetite, and anxiety.

Conference Call Information

Axsome will host a conference call and webcast today at 8:00 AM Eastern to discuss the expedited development plan for AXS-05 in the treatment of major depressive disorder following a Breakthrough Therapy meeting with the FDA. To participate in the live conference call, please dial (844) 698-4029 (toll-free domestic) or (647) 253-8660 (international), and use the conference ID 3977129. 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 FDA Breakthrough Therapy Designation

Breakthrough Therapy designation is granted by the FDA in order to expedite the development and review of drugs for serious or life-threatening conditions. In order to receive Breakthrough Therapy designation, a drug must demonstrate preliminary clinical evidence that the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. Breakthrough Therapy designation provides an organizational commitment involving senior managers from the FDA, more intensive FDA guidance on an efficient drug development program, and greater access to and more frequent communication with the FDA throughout the entire drug development and review process. It also provides the opportunity to submit sections of a New Drug Application (NDA) on a rolling basis, where the FDA may review portions of the NDA as they are received instead of waiting for the entire NDA submission. In addition, Breakthrough Therapy designated products are eligible for Priority Review, where the FDA has a goal to take action on an application within six months, as opposed to ten months under standard review. Breakthrough Therapy designation does not change the standards for approval.

About Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a debilitating, chronic, biologically-based disorder characterized by low mood, inability to feel pleasure, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms, and which impairs social, occupational, educational, or other important functioning. In severe cases, MDD can result in suicide. According to the National Institutes of Health, an estimated 7.1% of U.S. adults, or approximately 17.3 million, experience MDD each year[1]. According to the World Health Organization (WHO), depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease[2]. Nearly two-thirds of diagnosed and treated patients do not experience adequate treatment response with currently available first-line therapy[3], highlighting the need for additional therapies with new mechanisms of action. The majority of initial failures also fail second-line treatment. Patients diagnosed with MDD are defined as having treatment resistant depression (TRD) if they have failed to respond to two or more antidepressant therapies.

About AXS-05

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of major depressive disorder and other central nervous system (CNS) disorders. AXS-05 consists of dextromethorphan and bupropion and utilizes Axsome's metabolic inhibition technology. The dextromethorphan component of AXS-05 is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, which is a novel mechanism of action, meaning it works differently than currently available therapies for depression. The dextromethorphan component of AXS-05 is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. AXS-05 is covered by more than 30 issued U.S. and international patents which provide protection out to 2034. AXS-05 is 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 core CNS product candidate portfolio includes four clinical-stage candidates, AXS-05, AXS-07, AXS-09, and AXS-12. AXS-05 is currently in a Phase 3 trial in treatment resistant depression (TRD) and a Phase 2/3 trial in agitation associated with Alzheimer's disease (AD). AXS-05 is also being developed for major depressive disorder (MDD) and smoking cessation treatment. AXS-07 is currently in a Phase 3 trial for the acute treatment of migraine. AXS-12 is currently in a Phase 2 trial in narcolepsy. The Axsome Pain and Primary Care business unit (Axsome PPC) houses Axsome's pain and primary care assets, including AXS-02 and AXS-06, and intellectual property which covers these and related product candidates and molecules being developed by Axsome and others. AXS-02 is being developed for osteoporosis, the pain of knee osteoarthritis, and chronic low back pain. AXS-06 is being developed for osteoarthritis and rheumatoid arthritis. AXS-02, AXS-05, AXS-06, AXS-07, AXS-09, and AXS-12 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.

References

1. National Institute of Mental Health. (2017). Major Depression. Retrieved from https://www.nimh.nih.gov/health/statistics/major-depression.shtml.

2. World Health Organization. Fact Sheets: Depression.

3. Rush AJ, et al. (2007) Am J. Psychiatry 163:11, pp. 1905-1917 (STAR*D Study).

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, pace of enrollment 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, 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, but not limited to, FDA’s agreement with the Company’s plan to discontinue the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee’s recommendations); the potential for the ASCEND clinical trial to provide a basis for approval of AXS-05 for the treatment of major depressive disorder and accelerate its development timeline and commercial path to patients; 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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Source: Axsome Therapeutics, Inc.