Axsome Therapeutics Announces AXS-05 Achieves Primary Endpoint in Phase 2 Trial in Major Depressive Disorder

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- *Demonstrated statistically significant improvement in MADRS scores compared to active comparator (p<0.001 on primary endpoint)*
- *Rapid improvement in depressive symptoms demonstrating statistically significant superiority over active comparator within the first week (p=0.045 on CGI-I)*
- *Improvement with AXS-05 versus active comparator seen on multiple secondary endpoints, including remission in 47% of AXS-05 patients versus 16% of active comparator patients (p=0.004)*
- *Data support ongoing development of AXS-05 in treatment resistant depression and further development in MDD*
- *Potentially first-in-class, oral NMDA receptor antagonist with multimodal activity for the treatment of depression*
- *Company to host conference call at 8:30 AM ET*

NEW YORK, Jan. 07, 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 AXS-05, a novel, oral, investigational NMDA receptor antagonist with multimodal activity, met the prespecified primary endpoint and significantly improved symptoms of depression in the ASCEND Phase 2 trial in major depressive disorder (MDD). The ASCEND study is a randomized, double-blind, active-controlled, multi-center, U.S. trial, in which 80 adult patients with confirmed moderate to severe MDD were treated either with AXS-05 (45 mg dextromethorphan/105 mg bupropion), or the active comparator bupropion (105 mg), twice daily for 6 weeks.

AXS-05 met the prespecified primary endpoint by demonstrating a highly statistically significant reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, averaged over the 6-week treatment period (overall treatment effect), as compared to bupropion (p<0.001). At Week 6, AXS-05 demonstrated a 17.2 point reduction in the MADRS total score compared to a 12.1 point reduction for bupropion (p=0.013). AXS-05 rapidly reduced depressive symptoms, demonstrating a statistically significant improvement over bupropion on the Clinical Global Impression-Improvement scale (CGI-I) at Week 1 (p=0.045). Starting at Week 1, AXS-05 achieved numerical superiority over bupropion on the MADRS total score, with statistical significance achieved at Week 2 and maintained at all time points thereafter. At Week 6, 47% of patients who received AXS-05 achieved remission, prospectively defined as a score of 10 or less on the MADRS, compared with 16% of patients who received bupropion (p=0.004).

AXS-05 was superior to bupropion on multiple prespecified secondary endpoints, with statistically significant effects demonstrated on most, including the following: MADRS-6 (p=0.007 at Week 6); percentage of responders on MADRS-6 (response defined as ≥ 50% reduction from baseline) (p=0.014 at Week 6); CGI-I (p=0.045 at Week 1, and 0.051 at Week 6); Clinical Global Impression-Severity scale (CGI-S) (p=0.028 at Week 6); percentage of patients achieving remission on MADRS (remission defined as MADRS ≤10) (p=0.004 at Week 6). Additionally, the treatment effect observed with bupropion in the study was consistent with that observed in prior published trials.

“The clinically meaningful improvements in depressive symptoms seen with AXS-05 in this study were achieved versus an active comparator that is a well-established antidepressant, as early as only one week after initiation of treatment,” said Professor Maurizio Fava, MD, Executive Vice Chair, Department of Psychiatry, Massachusetts General Hospital (MGH) and Associate Dean for Clinical & Translational Research, Harvard Medical School. “Data show currently marketed antidepressants fail to provide adequate treatment response in about two thirds of treated patients. An estimated 16 million Americans suffer from major depressive disorder each year. As an oral NMDA receptor antagonist with multimodal activity, AXS-05 could provide a new approach to treating this potentially life-threatening condition.”

Fifty-one percent (51%) of patients in the trial had experienced three or more major depressive episodes prior to enrollment. Twenty-three percent (23%) of study participants had received first line treatment in their current major depressive episode prior to treatment with study medication.

AXS-05 was safe and well tolerated with no serious adverse events. The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. Overall, rates of adverse events were similar between AXS-05 and bupropion. Retention of patients in the study was favorable overall and higher in the AXS-05 treatment arm. There was no meaningful difference between the two treatment

arms in discontinuations due to adverse events. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or sexual dysfunction.

“The demonstration of a significant and rapid antidepressant effect with AXS-05, coupled with favorable safety, point to a differentiated clinical profile,” said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. “These data also suggest that AXS-05 has important biological activity and support the continued development of this novel multimodal agent in MDD as well as in other neuropsychiatric indications. These results build on the positive interim futility analyses for the Phase 3 trial of AXS-05 in treatment resistant depression and the Phase 2/3 trial of AXS-05 in Alzheimer’s disease agitation. The topline results of the ongoing Phase 3 trial of AXS-05 in treatment resistant depression, anticipated later this quarter, should add to the body of clinical data with AXS-05 in mood disorders.”

AXS-05 is a novel, oral, non-competitive NMDA receptor antagonist, also known as a glutamate receptor modulator, a new mechanism of action which is thought to help enhance synaptic connections and improve the communication between brain cells in people with major depressive disorder. In addition, AXS-05 enhances brain levels of serotonin, noradrenaline, and dopamine, which are key neurotransmitters involved in the regulation of mood; and displays anti-inflammatory properties, which may be relevant to treating MDD. The multimodal actions of AXS-05 may be complementary and synergistic for the treatment of this biologically-based condition. AXS-05 is covered by more than 30 issued U.S. and international patents providing protection out to 2034, and Axsome maintains worldwide rights.

“AXS-05 is an example of Axsome’s commitment to address significant unmet needs in CNS disorders through innovation. There have been no new significant pharmacological approaches in the treatment of depression over the past 30 years despite its growing contribution to the overall global burden of disease,” said Cedric O’Gorman, MD, Senior Vice President of Clinical Development and Medical Affairs of Axsome. “If approved, AXS-05 would be the first orally administered NMDA receptor antagonist, or glutamate receptor modulator, for the treatment of depression. This novel mechanism of action and AXS-05’s multimodal actions are different from the profile of all currently marketed antidepressants. We look forward to the continued evaluation of the potential of AXS-05 through our ongoing late stage clinical trials in multiple large indications with limited treatment options.”

The detailed results of the ASCEND trial are expected to be presented at upcoming scientific meetings. AXS-05 is also being evaluated in the STRIDE-1 Phase 3 trial in patients with treatment resistant depression (TRD), defined as patients with MDD who have failed two or more antidepressant treatments. AXS-05 was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) for the treatment of TRD. Given the results of the ASCEND trial, Axsome intends to meet with the FDA to define the potential regulatory path for the broader MDD population.

Summary of Topline Results of the ASCEND Trial

Effect on Depressive Symptoms

- AXS-05 was associated with a statistically significant mean reduction from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, calculated at each time point in the study and averaged, of 13.7 points for AXS-05 compared to 8.8 for bupropion ($p<0.001$).

- At Week 6, AXS-05 was associated with a statistically significant mean reduction from baseline in the MADRS total score of 17.2 points compared to a reduction of 12.1 points for bupropion ($p=0.013$).

- Remission, an absence of clinically significant symptoms of depression, prospectively defined as a MADRS total score of ≤ 10, was seen at Week 6 in 47% of patients who received AXS-05, compared to 16% of patients who received bupropion ($p=0.004$).

- Multiple other secondary endpoints improved in favor of AXS-05 with most achieving statistical significance (e.g. MADRS-6, CGI-I, CGI-S, etc.).

Time Course of Effect on Depressive Symptoms

- AXS-05 demonstrated a statistically significant reduction in total MADRS scores from baseline during the first two weeks of treatment as compared to bupropion ($p=0.01$).

- Numerical superiority of AXS-05 over bupropion for the reduction from baseline in the total MADRS score was seen at Week 1, with statistical significance achieved at Week 2 and at all time points thereafter. The effect was sustained as evidenced by a reduction, at Week 6, of 17.2 points for AXS-05 compared to a reduction of 12.1 points for bupropion ($p=0.013$).

- Remission rates were statistically significantly superior for AXS-05 as compared to bupropion starting at Week 2 ($p=0.004$) and at every time point thereafter including Week 6 ($p=0.004$).

- Improvement on the Clinical Global Impression-Improvement (CGI-I) scale was statistically significantly greater for AXS-05 as compared to bupropion at Week 1 ($p=0.045$); improvement with AXS-05 compared to bupropion on the CGI-I was also seen at Week 6 ($p=0.051$), with 59% of AXS-05 patients “Very Much Improved” compared to 27% of bupropion patients.

Safety and Tolerability

- AXS-05 was safe and well tolerated in the trial with similar rates of adverse events in the AXS-05 and bupropion arms.

- There were no serious adverse events, and there was no meaningful difference between the two treatment arms in discontinuations due to adverse events.

- The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety.

- Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

Conference Call Information

Axsome will host a conference call and webcast with slides today at 8:30 AM Eastern to discuss the topline results of the ASCEND trial of AXS-05 in major depressive disorder. To participate in the live conference call, please dial (844) 698-4029 (toll-free domestic) or (647) 253-8660 (international), and use the passcode 3792889. 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 the ASCEND Trial

ASCEND (Assessing Clinical Episodes in Depression) is a Phase 2, randomized, double-blind, active-controlled, multicenter trial of AXS-05 in patients with major depressive disorder (MDD) conducted in the United States. A total of 80 patients with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were randomized in a 1:1 ratio to receive AXS-05 (45 mg dextromethorphan/105 mg bupropion) (n=43), or bupropion (105 mg) (n=37), twice daily for 6 weeks. Prespecified efficacy analyses were conducted on this population on an intent-to-treat basis. The mean Montgomery-Åsberg Depression Rating Scale (MADRS) total scores at baseline were 31.8 for the AXS-05 group and 32.2 for the bupropion group. The study incorporated comprehensive blinding of investigators and patients to the confirmation of diagnosis. Patients without a confirmed diagnosis of moderate to severe MDD but who met all other entry criteria (n=17) were randomized for assessment of safety to maintain the blinding of study investigators, as prespecified. The prespecified primary endpoint of the study was the change from baseline in the MADRS total score, calculated at each time point in the study and averaged (overall treatment effect). Secondary endpoints included MADRS-6, Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), remission, safety and tolerability.

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 6.7% of U.S. adults, or approximately 16 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 the Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a commonly used, 10-item, validated rating scale used to provide an assessment of depression, and as a guide to evaluate recovery. This scale is an accepted regulatory endpoint for depression. The scale is used in clinical research to rate the severity of a patient’s depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms.

About AXS-05

AXS-05 is a novel, oral, investigational medicine 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), 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-12 is being developed for the treatment of the symptoms of 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 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 (“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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