Axsome Therapeutics Announces AXS-05 Achieves Primary Endpoint in GEMINI Phase 3 Trial in Major Depressive Disorder

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Demonstrated rapid, durable, and statistically significant improvement in depressive symptoms as measured by MADRS total score compared to placebo (p=0.002 on primary endpoint)

Statistically significant improvement at week 1 in MADRS total score compared to placebo (key secondary endpoint, p=0.007)

Statistically significant improvement versus placebo on all secondary endpoints at week 6, including remission (p<0.001), disease severity (p=0.002), functional impairment (p=0.002), and quality of life (p=0.011)

Positive results support NDA filing of AXS-05 for MDD, anticipated in 2H 2020

Potentially first-and-only, oral NMDA receptor antagonist with multimodal activity for the treatment of depression

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

NEW YORK, Dec. 16, 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 primary endpoint and rapidly and significantly improved symptoms of depression in the GEMINI Phase 3 trial in major depressive disorder (MDD). The GEMINI study was a randomized, double-blind, placebo-controlled, multi-center, U.S. trial, in which 327 adult patients with confirmed moderate to severe MDD were randomized to treatment with either AXS-05 (dextromethorphan/bupropion modulated delivery tablet) or placebo once daily for the first 3 days and twice daily thereafter for a total of 6 weeks.

AXS-05 met the primary endpoint by demonstrating a highly statistically significant reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared to placebo at Week 6, with mean reductions from baseline of 16.6 points for AXS-05 and 11.9 points for placebo (p=0.002). AXS-05 rapidly and durably improved depressive symptoms as compared to placebo with statistical significance on the MADRS total score demonstrated at Week 1, the earliest time point assessed, and at all time points thereafter. Rates of remission from depression (defined as MADRS ≤10) were statistically significantly greater for AXS-05 compared to placebo at Week 2 (p=0.013) and at every time point thereafter, being achieved by 39.5% of AXS-05 patients compared to 17.3% of placebo patients at Week 6 (p<0.001).

AXS-05 demonstrated rapid onset of action with statistically significant improvement as compared to placebo on numerous endpoints at Week 1, or only 4 days after the start of twice daily dosing. Statistically significant improvements at Week 1 were observed for MADRS total score (key secondary endpoint, p=0.007); Patient Global Impression-Improvement (PGI-I) (p=0.008); Clinical Global Impression-Severity (CGI-S) (p=0.013); Clinical Global Impression-Improvement (CGI-I) (p=0.035); Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR-16) (p=0.016); Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) (p=0.031); and other endpoints.

On all secondary endpoints including the following, AXS-05 demonstrated statistically significant improvement at Week 6 compared to placebo, reflecting increasing treatment effects over time: clinical response on the MADRS total score (defined as ≥50%) (p<0.001); PGI-I (p=0.007); CGI-S (p=0.002); CGI-I (p=0.016); QIDS-SR-16 (p=0.001); Sheehan Disability Scale (SDS) (p=0.002); and Q-LES-Q-SF (p=0.011).

"AXS-05 demonstrated a rapid and very clinically meaningful improvement in depressive symptoms, observed after only one week, in this large and well-controlled Phase 3 trial in major depressive disorder. Given the known challenges of conducting trials in psychiatry, it is very encouraging to see replication of Phase 2 findings in such a robust way," said Professor Maurizio Fava, MD, Psychiatrist-in-Chief at Massachusetts General Hospital (MGH), Director of the Division of Clinical Research of the MGH Research Institute, and Associate Dean for Clinical & Translational Research at Harvard Medical School. "Clinical depression is a potentially life-threatening condition. Currently marketed antidepressants fail to provide adequate treatment response in almost two thirds of treated patients, and may take up to six to eight weeks to provide clinically meaningful response. These data suggest that AXS-05, as an oral NMDA receptor antagonist with multimodal activity, may represent a novel treatment for major depressive disorder."

AXS-05 was well tolerated in the trial. The most commonly reported adverse events in the AXS-05 arm were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. There was one serious adverse event in the AXS-05 arm which was deemed by the investigator not to be study-drug related. The rates of discontinuation due to adverse events were low in both treatment groups (6.2% for AXS-05 and 0.6% for placebo). Treatment with AXS-05 was not associated with psychotomimetic effects or weight gain.

"We are very pleased with the compelling results of the GEMINI trial which demonstrate the potential for AXS-05 to provide significant benefits to patients living with depression, based on observed rapid and sustained antidepressant effects, resulting from its potentially first-in-class, oral NMDA receptor antagonist and multimodal mechanism of action," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "The progress of the AXS-05 clinical program in mood disorders reflects Axsome's commitment to accelerating innovation to address serious CNS disorders. With GEMINI and the previously completed ASCEND study, the efficacy of AXS-05 in major depressive disorder has now been demonstrated in two positive well-controlled trials, enabling the filing of an NDA for AXS-05, which is anticipated in the coming year."

AXS-05 was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in March 2019. Based on the outcome of the FDA Breakthrough Therapy meeting, Axsome believes the positive results of the GEMINI trial, along with the previously completed ASCEND trial of AXS-05 in MDD, are sufficient to support submission of a New Drug Application (NDA) for AXS-05 for the treatment of MDD. Axsome plans to file the NDA in the second half of 2020.

"Depression is a major public health concern with most patients failing to adequately respond to currently approved antidepressants," said Cedric

O'Gorman, MD, Senior Vice President of Clinical Development and Medical Affairs of Axsome. "The potentially fatal consequences of depression highlight the need to rapidly and effectively control depressive symptoms. The positive results of the GEMINI study are significant and exciting because they bring us closer to our goal of addressing this public health need with a potentially first-in-class, rapid-acting, effective, oral, antidepressant which can be safely administered at home. With its modulation of glutamate neurotransmission, if approved, AXS-05 would represent the first mechanistically novel oral pharmacotherapy for depression in over 30 years."

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 is a sigma-1 receptor agonist; 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 41 issued U.S. and international patents providing protection out to 2034, and Axsome maintains worldwide rights.

Detailed study results, including additional secondary endpoints, will be submitted for presentation at upcoming medical meetings and for publication. 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, and in the ADVANCE-1 trial in patients with Alzheimer's disease agitation. AXS-05 was granted Fast Track designations by the FDA for the treatment of TRD and for the treatment of Alzheimer's disease agitation.

Summary of Topline Results of the GEMINI 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 of 16.6 points for AXS-05 compared to 11.9 for placebo at Week 6 (p=0.002).
- Remission, an absence of clinically significant symptoms of depression, prospectively defined as a MADRS total score of ≤10, was seen at Week 6 in 39.5% of patients who received AXS-05, compared to 17.3% of patients who received placebo (p<0.001).
- Response, defined as a ≥50% improvement in the MADRS total score, was seen at Week 6 in 54.0% of patients who received AXS-05, compared to 34.0% of patients who received placebo (p<0.001).
- All secondary endpoints improved in favor of AXS-05 and achieved statistical significance at Week 6 (e.g. PGI-I, CGI-S, CGI-I, QIDS-SR-16, MADRS-6, etc.).

Time Course of Effect on Depressive Symptoms

- AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score of 7.3 points for AXS-05 compared to 4.9 points for placebo at Week 1 (p=0.007), with statistical significance for this measure maintained at all time points thereafter.
- Statistically significant improvements at Week 1 were also observed for the PGI-I (p=0.008), CGI-S (p=0.013), CGI-I (p=0.035), QIDS-SR-16 (p=0.016), MADRS-6 (p=0.019), and other endpoints. Statistically significant effects on these measures were generally maintained at all time points thereafter.
- Remission rates were statistically significantly greater for AXS-05 as compared to placebo at Week 2 (p=0.013) and at every time point thereafter.

Quality of Life and Functional Impairment

- AXS-05 was associated with a statistically significant improvement in quality of life, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), compared to placebo at Week 1 (p=0.031), and at every time point thereafter (p=0.011, at Week 6).
- AXS-05 was associated with a statistically significant reduction in functional impairment, as measured by the Sheehan Disability Scale (SDS), compared to placebo at Week 2 (p=0.003), and at every time point thereafter (p=0.002, at Week 6).

Safety and Tolerability

- AXS-05 was well tolerated in the trial.
- The most commonly reported adverse events in the AXS-05 arm were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. There was one serious adverse event in the AXS-05 arm which was deemed by the investigator not to be study-drug related.
- The rates of discontinuation due to adverse events were low in both treatment groups (6.2% for AXS-05 and 0.6% for

placebo).

- Treatment with AXS-05 was not associated with psychotomimetic effects or weight gain.

Conference Call Information

Axsome will host a conference call and webcast with slides today at 8:00 AM Eastern to discuss the topline results of the GEMINI 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 1022339. 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 GEMINI Trial

GEMINI (Glutamatergic and Monoaminergic Modulation in Depression) was a Phase 3, randomized, double-blind, multicenter, placebo-controlled trial of AXS-05 in patients with major depressive disorder (MDD) conducted in the U.S. A total of 327 patients with a confirmed diagnosis of moderate to severe MDD were randomized in a 1:1 ratio to receive AXS-05 (45 mg dextromethorphan/105 mg bupropion) (n=163), or placebo (n=164), twice daily for 6 weeks. The mean Montgomery-Åsberg Depression Rating Scale (MADRS) total scores at baseline were 33.6 for the AXS-05 group and 33.2 for the placebo group. The primary endpoint of the study was the change from baseline in the MADRS total score at Week 6. Secondary endpoints included MADRS change at Weeks 1 and 2, remission, response, Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Patient Global Impression-Improvement (PGI-I), MADRS-6, Sheehan Disability Scale (SDS), other quality of life measures, safety and tolerability. P-values were calculated based on least square mean estimates.

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 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 well-established, 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, patent-protected, 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 a proprietary formulation and dose 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 approved therapies for major depressive disorder. 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 41 issued U.S. and international patents which provide protection out to 2034. AXS-05 has been granted U.S. Food and Drug Administration (FDA) Breakthrough Therapy designation for the treatment of MDD. 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 3 trial in major depressive disorder (MDD), and a Phase 2/3 trial in agitation associated with Alzheimer's disease (AD). AXS-05 is also being developed for smoking cessation treatment. AXS-07 is currently in two Phase 3 trials for the acute treatment of migraine. AXS-12 is being developed for the treatment of narcolepsy. AXS-05, 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, accessed October 9, 2018, http://www.who.int/en/news-room/fact-sheets/detail/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 (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), 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, combined with the GEMINI clinical trial results, 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; the Company’s anticipated capital requirements, including the Company’s anticipated cash runway and the Company’s current expectations regarding its plans for future equity financings prior to the readout from its Phase 3 trials; 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. The data disclosed in this press release are considered topline data and subject to further statistical review and the final results may vary.

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