Axsome Therapeutics Announces Positive Results from the COMET-SI Trial of AXS-05 in Patients with Major Depressive Disorder Who Have Suicidal Ideation

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68% reduction in MADRS Suicidality Item score by Week 1, and 82% reduction by Week 4

Resolution of suicidal ideation achieved by 60% of patients by Week 1, and 78% by Week 4

Effects consistent with new integrated data from AXS-05 controlled trials demonstrating reduction in MADRS Suicidality Item score versus control, at Week 1 (p=0.001)

Rapid and substantial improvement in functioning achieved by 51% of patients at Week 1 and 77% of patients at Week 6 (Sheehan Disability Scale)

NEW YORK, Dec. 08, 2020 (GLOBE NEWSWIRE) -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders, today announced positive results from the open-label Phase 2 COMET-SI trial of AXS-05 in patients with major depressive disorder (MDD) who have suicidal ideation (SI). Patients treated with AXS-05 experienced rapid reduction of suicidal ideation, rapid functional improvement, and rapid, substantial, and durable improvements in overall depressive symptoms. The COMET-SI trial evaluated 37 patients with suicidal ideation, defined as a score of ≥3 on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI), at baseline. Patients were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) twice daily for up to 12 months. AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity.

A rapid reduction in suicidal ideation was observed with AXS-05 treatment, as demonstrated by reductions in the MADRS-SI score of 67.6% by Week 1, the earliest time point measured, 73.5% by Week 2, and 82.4% by Week 4. Resolution of suicidal ideation with AXS-05 treatment was achieved by 60.0% of patients by Week 1, 68.8% by Week 2, and 77.8% of patients by Week 4. Resolution was defined as a MADRS-SI score of 0 or 1 on a 0 to 6 scale.

The effect of AXS-05 on suicidal ideation in the open-label COMET-SI trial is consistent with new controlled data from the previously completed placebo-controlled GEMINI and active-controlled ASCEND trials of AXS-05 in the treatment of MDD. Integrated analysis from these trials demonstrated rapid reduction in MADRS-SI scores with AXS-05 compared to placebo or active control, which was statistically significant at Week 1, the earliest time point assessed (p=0.001 versus control).

The improvement in suicidal ideation with AXS-05 treatment in the COMET-SI trial was accompanied by rapid, substantial, and durable improvement in functional impairment, as measured by the Sheehan Disability Scale (SDS). The SDS is a patient-rated scale designed to assess function in work, social life, and family life, and is among the most commonly used function scales in depression clinical trials. Functional response on the SDS (defined as a total score of ≤12) was achieved after treatment with AXS-05 by 51.4% of patients at Week 1, 62.5% of patients at Week 2, and 76.9% of patients at Week 6.

Clinicians reported rapid, substantial, and durable global improvement in depression, measured by the Clinical Global Impression of Improvement (CGI-I) scale, in patients treated with AXS-05 in the COMET-SI trial. Marked or moderate improvement in depressive symptoms was achieved after treatment with AXS-05 by 40.0% of patients at Week 1, 59.4% of patients at Week 2, and 69.2% of patients at Week 6.

AXS-05 treatment in the COMET-SI trial also resulted in rapid, substantial, and durable improvement in depressive symptoms as measured by the MADRS total score. Patients experienced a mean reduction from baseline in the MADRS total score of 12.9 points at Week 1, 17.8 points at Week 2, and 22.8 points at Week 6. Clinical response on the MADRS (defined as ≥50% reduction in total score from baseline) was achieved after treatment with AXS-05 by 25.7% of patients at Week 1, 46.9% of patients at Week 2, and 69.2% of patients at Week 6. Remission from depression (defined as MADRS ≤10) was achieved after treatment with AXS-05 by 11.4% of patients at Week 1, 28.1% of patients at Week 2, and 50.0% of patients at Week 6.

“These early data are the first for AXS-05 in major depressive disorder patients with suicidal ideation, and highlight the rapid onset of action of AXS-05, observed by the first week, on clinically important measures in this serious condition” said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. “The results of the COMET-SI trial suggest that AXS-05, as an oral NMDA receptor antagonist, may provide unique benefits to patients by potentially rapidly and durably improving not only suicidal thoughts but also functional impairment associated with depression. These positive effects expand on and are consistent with the differentiated clinical profile of AXS-05 observed in our completed controlled trials in patients with major depressive disorder.”

AXS-05 was well tolerated in the COMET trial. The safety profile observed was consistent with what was previously reported in controlled trials of AXS-05 in MDD, with the most commonly reported adverse events being dizziness, nausea, headache, dry mouth, and decreased appetite.

COMET-SI Results Summary

A total of 37 patients with major depressive disorder (MDD) who had suicidal ideation at baseline were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) twice daily for up to 12 months. Suicidal ideation was defined as a score of ≥3 on the Suicidality Item of the Montgomery- Åsberg Depression Rating Scale (MADRS-SI) on a 0 to 6 scale. Topline results are summarized below:

- The mean MADRS-SI score was 3.4 at baseline. The mean MADRS total score was 36.8 at baseline. The mean Sheehan Disability Scale score was 21.2 at baseline.
- Treatment with AXS-05 was associated with reductions from baseline in the MADRS-SI score of 67.6% by Week 1, the

earliest time point assessed, 73.5% by Week 2, and 82.4% by Week 4 (mean point reductions of 2.3, 2.5, 2.8, respectively).

- Resolution of suicidal ideation, defined as a MADRS-SI score of 0 or 1, after treatment with AXS-05 was achieved by 60.0% of patients by Week 1, 68.8% of patients by Week 2, and 77.8% of patients by Week 4.
- Functional response on the Sheehan Disability Scale (defined as a total score of ≤12) after treatment with AXS-05, was achieved by 51.4% of patients at Week 1, 62.5% of patients at Week 2, and 76.9% of patients at Week 6.
- Marked or moderate improvement in depressive symptoms after treatment with AXS-05, assessed by the Clinical Global Impression of Improvement scale, was achieved by 40.0% of patients at Week 1, 59.4% of patients at Week 2, and 69.2% of patients at Week 6.
- Treatment with AXS-05 was associated with a mean reduction from baseline in the MADRS total score of 12.9 points at Week 1, 17.8 points at Week 2, and 22.8 points at Week 6.
- Clinical response on the MADRS (defined as ≥50% reduction from baseline) after treatment with AXS-05 was achieved by 25.7% of patients at Week 1, 46.9% of patients at Week 2, and 69.2% of patients at Week 6.
- Remission from depression (defined as MADRS ≤10) after treatment with AXS-05 was achieved by 11.4% of patients at Week 1, 28.1% of patients at Week 2, and 50.0% of patients at Week 6.

AXS-05 is a novel, oral, uncompetitive 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 depression. AXS-05 is also 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 depression. AXS-05 is covered by more than 93 issued U.S. and international patents providing protection out to 2040, and Axsome maintains worldwide rights. AXS-05 was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in March 2019.

About the COMET-SI Trial

The COMET-SI trial was a Phase 2, open-label study evaluating the efficacy and safety of AXS-05 in patients with major depressive disorder (MDD) who had suicidal ideation (SI), defined as a score of ≥3 on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI). Enrolled patients were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) twice daily for up to 12 months. Efficacy measures included the MADRS-SI score, the MADRS total score, Clinical Global Impression of Improvement (CGI-I), and the Sheehan Disability Scale (SDS).

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 Department of Health and Human Services, an estimated 7.8% of U.S. adults, or approximately 19.4 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 (dextromethorphan-bupropion modulated delivery tablet) 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 utilizes a proprietary formulation and dose of dextromethorphan and bupropion, and Axsome's metabolic inhibition technology, to modulate the delivery of the components. The dextromethorphan component of AXS-05 is an uncompetitive 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 93 issued U.S. and international patents which provide protection out to 2040. 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 biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders for which there are limited treatment options. For the many people facing unsatisfactory treatments for CNS disorders, Axsome accelerates the invention and adoption of life-changing medicines. Axsome's core CNS product candidate portfolio includes five clinical-stage candidates, AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14. AXS-05 is being developed for major depressive disorder (MDD), Alzheimer's disease (AD) agitation, and as a treatment for smoking cessation. AXS-07 is being developed for the acute treatment of migraine. AXS-12 is being developed for the treatment of narcolepsy. AXS-14 is being developed for fibromyalgia. AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14 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. Substance Abuse and Mental Health Services Administration. (2020). Results from the 2019 National Survey on Drug Use and Health. Retrieved from https://www.samhsa.gov/data/.
2. World Health Organization. Fact Sheets: Depression, accessed November 23, 2020, 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 discontinuation of the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee's recommendations); the potential for the MOMENTUM clinical trial to provide a basis for approval of AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment; 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; unforeseen circumstances or other disruptions to normal business operations arising from or related to COVID-19; 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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