Axsome Therapeutics Announces Positive Efficacy and Safety Results from Phase 3 COMET Long-Term Trial and COMET-AU Trial of AXS-05 in Major Depressive Disorder

December 1, 2020

Rapid and substantial improvement in depressive symptoms achieved by 40% of patients at 2 weeks, 73% at 6 weeks (MADRS response), and sustained over 12 months

Rapid and substantial improvement in functioning achieved by 55% of patients at 2 weeks, 71% at 6 weeks (Sheehan Disability Scale), and sustained over 12 months

Marked or moderate improvement in depression achieved by 50% of patients at 2 weeks, 83% at 6 weeks (Clinical Global Impression), and sustained over 12 months

Efficacy in patients failing one prior antidepressant similar to overall results

Long-term safety profile consistent with previously completed controlled trials, with no new safety signals detected

NDA on track for submission in January 2021

NEW YORK, Dec. 01, 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 long-term, open-label Phase 3 COMET trial of AXS-05 in patients with major depressive disorder (MDD), and the open-label Phase 2 COMET-AU trial in patients failing one prior antidepressant treatment. AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. Patients treated with AXS-05 in these trials experienced rapid, substantial, and durable improvements in depressive symptoms and functional impairment that was sustained over the 12-month treatment period. AXS-05 was well tolerated over the long-term treatment period with a safety profile consistent with what was observed in the previously reported controlled trials in terms of frequency and type of adverse events, with no new safety signals detected. Axsome remains on track to submit an NDA for AXS-05 in the treatment of MDD in January 2021.

“The data from the open-label Phase 3 COMET trial indicate that AXS-05 treatment is associated with rapid improvement in both depressive symptoms and related functional impairment that are sustained with long-term treatment and accompanied by a favorable safety profile,” said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. “Results from the open-label Phase 2 COMET-AU trial further indicate that the treatment benefits with AXS-05 were also substantial in patients who were unresponsive to a prior antidepressant. Overall, the short and long-term efficacy and safety data from these real-world studies add to the differentiated clinical profile of AXS-05, and are consistent with those observed in our previously reported double-blind efficacy trials.”

The COMET (Clinical Outcomes with NMDA-based Depression Treatment) trial evaluated the efficacy and safety of AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) in patients with MDD who were treated twice daily for up to 12 months. A total of 876 patients were enrolled, consisting of 265 patients who rolled over from prior controlled trials with AXS-05 (roll-over patients), and 611 new (de novo) patients who had not previously participated in an AXS-05 trial. The trial was concluded once at least 300 patients had been treated for 6 months and approximately 100 patients had been treated for 12 months, as pre-specified. At the time of study conclusion, 597 patients had reached at least 6 months, and 110 patients had reached at least 12 months of treatment. The COMET-AU trial evaluated 115 patients with antidepressant unresponsive (AU) MDD, defined as patients with ongoing symptoms of depression despite previously receiving one standard antidepressant pharmacotherapy. Safety results discussed below include all patients enrolled in the COMET trial. Efficacy results from the overall COMET trial presented below are for de novo patients only (n=611). Maintenance of efficacy results for roll-over patients were similar, demonstrating sustained efficacy over 12 months, and will be presented in future scientific publications.

In the overall COMET trial, AXS-05 treatment resulted in rapid, substantial, and durable improvement in depressive symptoms, measured using the Montgomery-Åsberg Depression Rating Scale (MADRS), which was sustained or increased with long-term treatment. Patients experienced mean reductions from baseline in the MADRS total score of 14.0 points at Week 2 and 21.1 points at Week 6 (primary timepoint). Reductions from baseline at 6 and 12 months were 23.9 points and 23.0 points, respectively.

Clinical response on the MADRS (defined as ≥50% reduction from baseline) after treatment with AXS-05 was achieved by 39.7% of patients at Week 2 and 73.2% of patients at Week 6. This rate of response was sustained or increased with long-term treatment, with 84.6% and 82.8% of patients achieving a clinical response at 6 and 12 months, respectively. Remission from depression (defined as MADRS ≤10) after treatment with AXS-05 was achieved by 21.5% of patients at Week 2 and 52.5% of patients at Week 6. This rate of remission was sustained or increased with long-term treatment, with 68.7% and 69.0% of patients in remission at 6 and 12 months, respectively.

Clinicians reported rapid, substantial, and durable global improvement in depressive symptoms, measured by the Clinical Global Impression of Improvement (CGI-I) scale, in patients treated with AXS-05. Marked or moderate improvement in depressive symptoms was achieved after treatment with AXS-05 by 50.4% of patients at Week 2 and 83.1% of patients at Week 6. This improvement on the CGI-I was sustained or increased with long-term treatment, as evidenced by marked or moderate improvement being achieved by 86.7% and 93.1% of patients at 6 and 12 months, respectively.

Patients experienced rapid, substantial, and durable improvement in functional impairment, as measured by the Sheehan Disability Scale (SDS) with AXS-05 treatment. The SDS is a patient-rated scale that was designed to assess functioning in work, social life, and family life, and is among the most commonly used functional impairment scales in depression clinical trials. Clinical response on the SDS (defined as a total score of ≤12) was achieved after treatment with AXS-05 by 55.1% of patients at Week 2 and 70.7% of patients at Week 6. This improvement in functioning was maintained or increased with long-term treatment with AXS-05, as evidenced by clinical response on the SDS being achieved by 80.6% and 75.9% of patients at 6

months and at 12 months, respectively.

Results of the COMET-AU trial were similar to those of the overall COMET study, demonstrating rapid, substantial, and durable improvements in depressive symptoms and functional impairment with AXS-05 treatment in patients who had failed one prior antidepressant treatment. Mean reductions from baseline in the MADRS total score were 13.1 points at Week 2 and 19.1 points at Week 6. Clinical response on the MADRS was achieved by 33.3% of patients at Week 2 and 64.6% of patients at Week 6. Remission from depression was achieved by 15.7% of patients at Week 2 and 40.4% of patients at Week 6. Marked or moderate improvement in depressive symptoms, assessed by the CGI-I scale, was achieved by 40.7% of patients at Week 2 and 70.0% of patients at Week 6. Clinical response on the SDS was achieved by 48.1% of patients at Week 2 and 63.4% of patients at Week 6. The improvements in depressive symptoms and functioning were sustained with long-term treatment.

AXS-05 was well tolerated with long-term dosing. The safety profile of AXS-05 over the 12-month treatment period was consistent with what was previously reported in short-term controlled trials, with no new safety signals detected. The most commonly reported adverse events in the COMET trial were dizziness (12.7%), nausea (11.9%), headache (8.8%), dry mouth (7.1%), and decreased appetite (6.1%). These adverse events occurred at rates that were similar to those observed in the previously reported controlled trials with AXS-05. During the 12-month trial, 8.4% of patients discontinued due to adverse events, with no individual adverse event in more than 1.5% of patients. Treatment with AXS-05 was not associated with psychotomimetic effects, cognitive impairment, weight gain, or increased sexual dysfunction.

COMET Efficacy Results Summary

A total of 611 de novo patients with MDD were enrolled and treated with AXS-05 twice daily for up to 12 months. Efficacy results for these patients are summarized below:

- The mean MADRS total score was 32.7 at baseline.
- Treatment with AXS-05 was associated with a mean reduction from baseline in the MADRS total score of 9.1 points at Week 1, 14.0 points at Week 2, and 21.1 points at Week 6. Mean MADRS total score reductions from baseline after 6 and 12 months of treatment with AXS-05 were 23.9 points and 23.0 points, respectively.
- Clinical response on the MADRS (defined as ≥50% reduction from baseline) after treatment with AXS-05 was achieved by 18.8% of patients at Week 1, 39.7% of patients at Week 2, and 73.2% of patients at Week 6. Clinical response on the MADRS total score after 6 and 12 months of treatment with AXS-05 was achieved by 84.6% and 82.8%, respectively.
- Remission from depression (defined as MADRS ≤10) after treatment with AXS-05 was achieved by 8.3% of patients at Week 1, 21.5% of patients at Week 2, and 52.5% of patients at Week 6. Remission from depression after 6 and 12 months of treatment with AXS-05 was achieved by 68.7% and 69.0% of patients, respectively.
- Marked or moderate improvement in depressive symptoms after treatment with AXS-05, assessed by the Clinical Global Impression of Improvement (CGI-I) scale, was achieved by 27.0% of patients at Week 1, 50.4% of patients at Week 2, and 83.1% of patients at Week 6. Marked or moderate improvement after 6 and 12 months of treatment with AXS05 was achieved by 86.7% and 93.1% of patients, respectively.
- Clinical response on the Sheehan Disability Scale (SDS) (defined as a total score of ≤12) after treatment with AXS-05, was achieved by 42.9% of patients at Week 1, 55.1% of patients at Week 2, and 70.7% of patients at Week 6. Clinical response on the SDS after 6 and 12 months of treatment with AXS-05 was achieved by 80.6% and 75.9% of patients, respectively.

COMET-AU Efficacy Results Summary

A total of 115 patients with antidepressant unresponsive (AU) MDD, defined as patients with ongoing symptoms of depression despite previously receiving one standard antidepressant pharmacotherapy were enrolled and treated with AXS-05 twice daily for up to 12 months. Efficacy results for these patients are summarized below:

- The mean MADRS total score was 33.3 at baseline.
- Treatment with AXS-05 was associated with a mean reduction from baseline in the MADRS total score of 9.4 points at Week 1, 13.1 points at Week 2, and 19.1 points at Week 6. Mean MADRS total score reduction from baseline after 6 months of treatment with AXS-05 was 21.6 points.
- Clinical response on the MADRS total score (defined as ≥50% reduction from baseline) after treatment with AXS-05 was achieved by 18.8% of patients at Week 1, 33.3% of patients at Week 2, and 64.6% of patients at Week 6. Clinical response on the MADRS total score after 6 months of treatment with AXS-05 was achieved by 74.3%.
- Remission from depression (defined as MADRS ≤10) after treatment with AXS-05 was achieved by 8.9% of patients at Week 1, 15.7% of patients at Week 2, and 40.4% of patients at Week 6. Remission from depression after 6 months of treatment with AXS-05 was achieved by 55.4%.
- Marked or moderate improvement in depressive symptoms after treatment with AXS-05, assessed by the Clinical Global

Impression of Improvement (CGI-I) scale, was achieved by 24.1% of patients at Week 1, 40.7% of patients at Week 2, and 70.0% of patients at Week 6. Marked or moderate improvement after 6 months of treatment with AXS-05 was achieved by 71.6%.

- Clinical response on the Sheehan Disability Scale (SDS) (defined as a total score of ≤12) after treatment with AXS-05, was achieved by 35.7% of patients at Week 1, 48.1% of patients at Week 2, and 62.4% of patients at Week 6. Clinical response on the SDS after 6 months of treatment with AXS-05 was achieved by 62.2%.

Long-Term Safety and Tolerability

Safety results are for all patients enrolled in the COMET trial (n=876). Safety results for the 12-month treatment period are summarized below:

- AXS-05 was well tolerated with a safety profile that was consistent with what was previously reported in short-term controlled trials, with no new safety signals detected.
- The most commonly reported adverse events were dizziness (12.7%), nausea (11.9%), headache (8.8%), dry mouth (7.1%), and decreased appetite (6.1%), which occurred at rates that were similar to those observed in the previously reported controlled trials with AXS-05.
- Discontinuations due to adverse events occurred in 8.4% of patients during the 12-month trial, with no individual event occurring in more than 1.5% of patients.
- Treatment with AXS-05 was not associated with psychotomimetic effects, cognitive impairment, weight gain, or increased sexual dysfunction.

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 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 and COMET-AU Trials

COMET (Clinical Outcomes with NMDA-based Depression Treatment) was a Phase 3, open-label trial to evaluate the long-term safety and efficacy of AXS-05 in patients with major depressive disorder (MDD). Enrolled patients were treated with AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) twice daily for up to 12 months. The COMET-AU trial was a Phase 2, open-label sub-study evaluating the efficacy and safety of AXS-05 in patients with antidepressant unresponsive (AU) MDD. Efficacy measures included the Montgomery-Åsberg Depression Rating Scale (MADRS), 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 National Institutes of Health, 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 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 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. National Institute of Mental Health. (2020). Major Depression. Retrieved from https://www.nimh.nih.gov/health/statistics/major-depression.shtml.
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.

Axsome Contact:
Mark Jacobson
Chief Operating Officer
Axsome Therapeutics, Inc.
22 Cortlandt Street, 16th Floor
New York, NY 10007
Tel: 212-332-3243
Email: mjacobson@axsome.com
www.axsome.com

Source: Axsome Therapeutics, Inc.