Esketamine Phase 2 Data Published in JAMA Psychiatry Showed Significant Improvement of Depressive Symptoms in People with Treatment-Resistant Depression

TITUSVILLE, N.J., Dec. 28, 2017 /PRNewswire/ -- Janssen Research & Development, LLC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, announced that data from a Phase 2 clinical study of intranasal esketamine, published yesterday in *JAMA Psychiatry*, showed a significant, clinically meaningful, rapid improvement of depressive symptoms as compared to intranasal placebo, in patients with treatment-resistant depression. During the study, all participants continued to take the oral antidepressants, considered to be standard of care, that they were taking at study entry. Change in the Montgomery-Asberg Depression Rating Scale (MADRS) total scores, measured in the study, demonstrated the improvement in patients' depressive symptoms. Decreases in MADRS total score indicate clinical improvement.

Esketamine belongs to a new class of investigational medicines in psychiatry known as glutamate receptor modulators that may help restore synaptic connections in brain cells in people with major depressive disorder. In this study, treatment-resistant depression was defined as a lack of clinically meaningful improvement after treatment with at least two different oral antidepressant treatments taken at adequate doses, at least one of which was taken during the patient's current major depressive episode.

The antidepressant effect was observed with all three doses studied, evident as early as two hours post dose, and was dose related. Symptom improvement was observed after one week with intranasal esketamine for all three doses (28 mg, 56 mg and 84 mg), administered twice weekly, with a significant ascending dose-response relationship ($p<0.001$). Improvement appeared to be sustained with reduced dosing frequency for up to nine weeks in the open label treatment phase.

The study drug was provided in disposable nasal spray devices containing 200 µl of solution (i.e., two sprays), and administered under the supervision of a health care professional.

"About one third of patients with major depressive disorder do not respond to current treatment options," said Husseini K. Manji, MD, Global Head, Neuroscience Therapeutic Area, Janssen. "The results of this study reinforce the potential of esketamine as a treatment for patients with treatment-resistant depression and support further clinical research, providing hope for people in need. If approved by the FDA, esketamine would be one of the first new approaches to treat refractory major depressive disorder available to patients in the last 50 years."

The primary efficacy endpoint in the study was change from baseline to day eight (for both of two one-week treatment periods in the study) in MADRS total score. Change in MADRS total score (both periods combined) in all three esketamine treatment groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], $p=0.02$; 56 mg: -6.3 [2.07], $p=0.001$; 84 mg: -9.0 [2.13], $p<0.001$), with a significant ascending dose-response relationship ($p<0.001$). Response was

observed as early as two hours post dose and appeared to increase over time with repeated dosing, as evidenced by a decrease in mean MADRS total score over the open-label phase (mean [SE] change from open-label baseline to day 74: -7.2 [1.84]). Among those who received the same treatment and completed the two-week double-blind phase, more participants treated with the two higher esketamine doses, as compared to placebo, remitted after two weeks of treatment (12.5%, 27.3%, and 40.0% in the 28 mg, 56 mg and 84 mg groups, respectively, and 10.0%, in the placebo group). In addition, improvement in mean MADRS ratings persisted over the eight-week follow-up phase (without additional esketamine doses) in those participants who remained in the study.

Intranasal esketamine appeared to be generally well-tolerated based on the adverse event data from this study. Three (of 56, 5%) esketamine-treated participants during the double-blind phase (versus 0 placebo) and one (of 57, 2%) during the open-label phase had adverse events that led to discontinuation of their participation in the study. There were no deaths during this study. The majority of adverse events occurring on dosing days were transient (resolved within two hours of dosing) and either mild or moderate in severity. The three most common treatment-emergent adverse events observed among esketamine-treated participants during the double-blind phase were dizziness, headache, and perceptual changes/dissociative symptoms; the frequency of each was >2-fold higher for esketamine than for placebo. Other adverse events included dysgeusia (metallic or bad taste) and sedation.

Esketamine is currently being evaluated in Phase 3 clinical studies for treatment-resistant depression and for patients with major depressive disorder who are at imminent risk for suicide. There is also a Phase 2 clinical study for adolescents with major depressive disorder who are at imminent risk for suicide.

About the Study
This Phase 2, double-blind, doubly-randomized, placebo-controlled, multicenter study (13 sites in the US, 1 in Belgium) was conducted from January 2014 to September 2015. It enrolled 126 adults (20 to 64 years) who were medically stable and had received a diagnosis of major depressive disorder, according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – text revised (DSM-IV-TR). All enrollees had a history of inadequate response to ≥2 antidepressants (i.e., TRD). Of the 126 patients screened, 67 were randomized, and 60 completed the two-week double-blind phase.

The study consisted of four phases: 1) screening, 2) double-blind treatment (days 1 to 15), comprised of two 1-week periods (Period 1, Period 2), 3) optional open-label treatment (days 15 to 74) with tapering of intranasal dosing frequency, and 4) post-treatment follow-up (8 weeks).

In Period 1, participants were randomized [3:1:1:1] to placebo (n=33), esketamine 28 (n=11), 56 (n=11), or 84 mg (n=12) twice-weekly; in Period 2, 28 placebo-treated participants with moderate-to-severe depressive symptoms were re-randomized [1:1:1:1] to one of the four treatment arms; those with mild symptoms continued on placebo. During the open-label phase, dosing frequency was reduced from twice-weekly to weekly, then every two weeks.

Efficacy data were analyzed in intent-to-treat (ITT) analysis sets for each period and phase. The ITT analysis sets included all participants who received at least one dose of study medication during that period or phase and had baseline and at least one post baseline MADRS total score within that period or phase.

For additional study information, visit ClinicalTrials.gov.

About Esketamine
Esketamine for intranasal administration is an investigational compound being studied by Janssen Research & Development, LLC as part of a global development program. Esketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which has a novel mechanism of action, meaning it works differently than currently available therapies for depression.

Esketamine received Breakthrough Therapy Designations from the U.S. Food and Drug Administration (FDA) in November 2013 for treatment-resistant depression and in August 2016 for the indication of major depressive disorder with imminent risk for suicide.

About Major Depressive Disorder
Major depressive disorder affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide.[1] Individuals with depression, including major depressive disorder, experience continuous suffering from a serious, biologically based disease which has a significant negative impact on all aspects of life, including quality of life and function.[2] Although currently available antidepressants are effective for some patients, about one third of patients do not respond to treatment and are thought to have treatment-resistant depression.[3]

About the Janssen Pharmaceutical Companies
At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenUS and www.twitter.com/JanssenGlobal.

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[1] http://www.who.int/mediacentre/factsheets/fs369/en/
[2] Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: Results from the Medical Outcomes Study. *JAMA*. 1989; 262(7):914–919.
[3] Thase ME. Update on partial response in depression. J Clin Psychiatry. 2009;70[suppl 6]:4-9.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development and the potential benefits of esketamine. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; competition, including technological advances, new products and patents attained by competitors; challenges to patents; manufacturing difficulties and delays; changes in behavior and spending patterns or financial distress of purchasers of health care products and services;

changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and description of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 1, 2017, including in Exhibit 99 thereto, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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