Janssen Announces Results of Esketamine Nasal Spray Phase 3 Study in Patients with Treatment-Resistant Depression

September 21, 2018

TITUSVILLE, N.J., Sept. 21, 2018 /PRNewswire/ -- The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results from a Phase 3 clinical study of the investigational product esketamine nasal spray in patients with treatment-resistant depression. Janssen researchers presented these results at the Ninth Biennial Conference of the International Society for Affective Disorders (ISAD) and the Houston Mood Disorders Conference, taking place September 20-22, 2018 in Houston, TX.

This clinical trial was a randomized, double-blind study of two fixed doses of esketamine, 56 mg and 84 mg. The study did not demonstrate statistical significance for the primary endpoint, change in a depression severity rating scale score from baseline to four weeks, for esketamine 84 mg plus oral antidepressant compared to oral antidepressant plus placebo. Therefore, based on the prespecified analysis plan, the esketamine 56 mg plus oral antidepressant group could not be formally evaluated in this study.

Importantly, results of analyses of the primary endpoint and key secondary endpoints numerically favored both esketamine plus oral antidepressant treatment groups over the oral antidepressant plus placebo group.

"Together with the recently announced results from four other Phase 3 studies, these data provide continued support for a positive benefit-risk assessment for esketamine nasal spray as a potentially novel treatment approach for patients living with treatment-resistant depression," said Husseini K. Manji, M.D, Global Head, Neuroscience Therapeutic Area, Janssen Research & Development, LLC. "One-third of patients with major depressive disorder do not respond to existing therapies, and they need new treatment options." [1]

Janssen announced on September 4, 2018 that it submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for esketamine.[2] Janssen is seeking FDA approval of esketamine for treatment-resistant depression in adults. The NDA is based on five pivotal Phase 3 studies of esketamine in patients with treatment-resistant depression: three short-term studies; one withdrawal maintenance of effect study; and one long-term safety study. Data from these studies demonstrate that treatment with esketamine plus a newly initiated oral antidepressant compared to placebo plus a newly initiated antidepressant was associated with rapid reduction of depressive symptoms and delayed time to relapse of symptoms of depression.[3,4] The long-term safety study showed that the esketamine doses studied were generally tolerated, with no new safety signals with dosing up to 52 weeks.[5]

This study defined treatment-resistant depression as patients who had not responded to two or more antidepressants of adequate dose and duration in the current episode of depression.

The results of this study showed that esketamine plus an oral antidepressant demonstrated safety and tolerability consistent with safety results reported in earlier esketamine Phase 2 and Phase 3 studies.[6]

Study Design
The study was an international, Phase 3, double-blind, active-controlled, multi-center study of 346 adults with treatment-resistant depression. Its purpose was to evaluate the efficacy and safety of fixed doses of esketamine plus an oral antidepressant. The primary objective was to evaluate the efficacy of switching adult patients with treatment-resistant depression from a prior antidepressant treatment (to which they had not responded) to a fixed dose of esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant plus placebo, in improving depressive symptoms. Improvement in symptoms was assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from day one (pre-randomization) to the end of the four-week double-blind induction phase.

Primary Efficacy Endpoint
Results of the study were based on a mixed-effects model for repeated measures (MMRM) analysis of change in MADRS total score from baseline to day 28. The results numerically favored both esketamine plus an oral antidepressant groups over the oral antidepressant plus placebo group. The median unbiased estimate of the difference (95% confidence interval) between esketamine 84 mg plus oral antidepressant and the oral antidepressant plus placebo treatment groups was -3.2 (-6.88, 0.45), and that of esketamine 56 mg plus oral antidepressant and the oral antidepressant plus placebo treatment groups was -4.1 (-7.67, -0.49).

Using a weighted combination test, the difference between the esketamine 84 mg plus oral antidepressant group and oral antidepressant plus placebo group was not statistically significant (two-sided p=0.088). Therefore, in accordance with the predefined testing sequence, esketamine 56 mg plus oral antidepressant treatment group could not be formally evaluated.

Secondary Efficacy Endpoints

The key secondary endpoints included onset of clinical response by day two, and change from baseline to day 28 in total scores from the Sheehan Disability Scale (SDS), a subject-reported outcome measure widely used and accepted for assessment of functional impairment and associated disability, and Patient Health Questionnaire-9 (PHQ-9), a self-report scale assessing depressive symptoms. These endpoints could not be formally evaluated due to the predefined testing sequence, however the proportion of subjects with onset of clinical response by day two maintained to four weeks was numerically higher, and the change in SDS and PHQ-9 total scores at day 28 numerically favored, both esketamine plus oral antidepressant groups compared to the oral antidepressant plus placebo group.

As observed in the other Phase 3, short-term studies of esketamine, overall response rates (≥50% improvement from baseline) and remission rates (MADRS total score ≥12) at day 28 were higher for both esketamine plus oral antidepressant groups compared with the oral antidepressant plus placebo group. Response rate at day 28 was 53.1% and 54.1% in patients treated with esketamine 84 mg plus oral antidepressant and 56 mg plus oral antidepressant, respectively, compared to 38.9% for oral antidepressant plus placebo. Remission rate at day 28 was 38.8% and 36.0% in patients treated with esketamine 84 mg plus oral antidepressant and 56 mg plus oral antidepressant, respectively, compared to 30.6% with placebo plus oral antidepressant.

Safety Results
Safety results were consistent with previously reported findings from completed Phase 2 and 3 studies of esketamine. There were no clinically meaningful differences in safety between the esketamine 56 mg plus oral antidepressant and esketamine 84 mg plus oral antidepressant groups, and no new or dose-related safety concerns were identified.

Most adverse events were mild or moderate in severity, and were typically observed on nasal spray dosing days, and generally resolved the same day. The most common treatment-emergent adverse events (TEAEs) (reported by ≥10% of study patients) in the esketamine 84 mg plus oral antidepressant group during the double-blind induction phase were nausea, dissociation, dizziness, headache, vertigo, somnolence (sleepiness), dysgeusia (taste disturbance), hypoesthesia (diminished sense of touch or sensation), vomiting, and hypoesthesia oral; and in the esketamine 56 mg plus oral antidepressant group were dizziness, nausea, dissociation, somnolence, vertigo, headache, paresthesia (tingling sensation), dysgeusia, hypoesthesia oral, hypoesthesia, and fatigue. A slightly higher incidence of severe events of dissociation and nausea was observed in the esketamine 84 mg plus oral antidepressant treatment group as compared to the esketamine 56 mg plus oral antidepressant treatment group.

More information about this Phase 3 study of esketamine plus oral antidepressant can be found at the link below:

https://clinicaltrials.gov/ct2/show/NCT02417064

About Esketamine
Esketamine nasal spray is an investigational product being studied by Janssen Research & Development, LLC as part of a global development program. Esketamine is a glutamate receptor modulator, thought to help restore synaptic connections in brain cells in people with major depressive disorder. It has a novel mechanism of action, meaning it works differently than currently available therapies for major depressive disorder.

The U.S. FDA has granted Breakthrough Therapy Designations for esketamine for treatment-resistant depression and for a second indication, major depressive disorder with imminent risk for suicide.[7]

About Treatment-Resistant Depression
Major depressive disorder affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide. 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.[8] Although currently available antidepressants are effective for many patients, about one-third of patients do not respond to treatment and are thought to have treatment-resistant depression.[1]

About the Janssen Pharmaceutical Companies of Johnson & Johnson
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. Janssen Research & Development, LLC is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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 December 31, 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.

1. National Institute of Mental Health. Questions and Answers about the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study — Background. Available at:https://www.nimh.nih.gov/funding/clinical-research/practical/stard/backgroundstudy.shtml. Accessed September 2018.

2. Johnson & Johnson Press Release. Janssen Submits Esketamine Nasal Spray New Drug Application to U.S. FDA for Treatment-Resistant Depression. Available at: https://www.jnj.com/janssen-submits-esketamine-nasal-spray-new-drug-application-to-u-s-fda-for-treatment-resistant-depression. Accessed September 2018.
3. V Popova, EJ Daly, M Trivedi, K Cooper, R Lane, P Lim, C Mazzucco, D Hough, ME Thase, RC Shelton, P Molero, E Vieta, M Bajbouj, H Manji, WC Drevets, JB Singh. Randomized, Double-Blind Study of Flexibly Dosed Intranasal Esketamine Plus Oral Antidepressant Versus Active Control in Treatment-Resistant Depression. Poster presented at: 2018 Annual Meeting of the American Psychiatric Association (APA); May 2018; New York, New York.
4. EJ Daly, M Trivedi, A Janik, H Li, Y Zhang, X Li, R Lane, P Lim, AR Duca, D Hough, ME Thase, J Zajecka, A Winokur, I Divacka, A Fagiolini, WJ Cubala, I Bitter, P Blier, RC Shelton, P Molero, H Manji, WC Drevets, JB Singh. A Randomized Withdrawal, Double-blind, Multicenter Study of Esketamine Nasal Spray Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression. Poster presented at: The American Society of Clinical Psychopharmacology; May 2018; Miami, Florida.
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7. Johnson & Johnson Press Release. Esketamine Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for Major Depressive Disorder with Imminent Risk for Suicide. Available at: https://www.jnj.com/media-center/press-releases/esketamine-recieves-breakthrough-therapy-designation-from-us-food-and-drug-administration-for-major-depressive-disorder-with-imminent-risk-of-suicide. Accessed September 2018.
8. World Health Organization. Depression. Available at: http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed September 2018.

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