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New Phase 3 Data Show Esketamine Nasal Spray Demonstrated Rapid Improvements in Depressive Symptoms in Patients with Treatment-Resistant Depression

- *Study in adults with treatment-resistant depression marks the first time an antidepressant has achieved superiority in a clinical trial for major depressive disorder that included a newly initiated oral antidepressant in both the control and placebo groups*
- *Study in elderly patients is the first clinical trial conducted in treatment-resistant depression in this population*

BEERSE, BELGIUM, 5th May, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the results from two Phase 3 clinical studies of the investigational compound esketamine nasal spray in patients with treatment-resistant depression. These studies will be presented at the American Psychiatric Association Annual Meeting, taking place May 5-9 in New York, NY.^{1,2}

Data from a study in adults with treatment-resistant depression showed that flexibly dosed esketamine nasal spray plus a newly initiated oral antidepressant demonstrated a statistically significant, clinically meaningful, rapid reduction of depressive symptoms compared to placebo nasal spray plus a newly initiated oral antidepressant. The study defined treatment-resistant as patients who had not responded to two or more currently available antidepressants of adequate dose and duration in the current episode of depression. The most common treatment-emergent adverse events reported (>10% of patients) in the esketamine group were metallic taste, nausea, vertigo, dizziness, headache, drowsiness, short lived perceptual changes, blurred vision, paraesthesia (tingling sensation) and anxiety. The most common treatment-emergent adverse events (>10% of patients) reported in the placebo group were metallic taste and headache.

Data from a second study, in elderly patients aged 65 years and older with treatment-resistant depression, which is the first study of its kind in this population, showed treatment with flexibly dosed esketamine plus a newly initiated oral antidepressant demonstrated clinically meaningful effects compared to placebo nasal spray plus a newly initiated oral antidepressant. However, the study narrowly missed statistical significance for its primary efficacy endpoint. Safety results were consistent with previous studies of esketamine in younger adult populations. The most common treatment-emergent adverse events reported (>10% of patients) in the esketamine group were dizziness, nausea, headache, fatigue, increased blood pressure, vertigo and short lived perceptual changes. There were no treatment-emergent adverse events reported in >10% of patients in the placebo group.

“With about 30 percent of patients with major depression failing to respond to currently available antidepressants³, treatment-resistant depression represents a major public health need,” said Hussein K. Manji, MD, Global Head, Neuroscience Therapeutic Area, Janssen Research & Development, LLC. “The positive Phase 3 results for esketamine nasal spray in adults with treatment-resistant depression are exciting, particularly as they mark the first time an antidepressant has achieved superiority versus an active comparator in any clinical trial for major depressive disorder. What makes this significant is that the response was rapid and this milestone was achieved in patients deemed to be treatment-resistant. We are also pleased with the clinically meaningful outcomes for esketamine nasal spray in elderly patients, a population that often has greater disability and lower response rates.”

“There’s a critical need for new, rapidly acting and effective treatment options for people with major depressive disorder who do not respond to existing therapies,” said Mathai Mammen, M.D., Ph.D., Global Head, Janssen Research & Development, LLC. “Janssen is fully committed to exploring the newest science in the area of mood disorders and bringing these discoveries to patients in need.”

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Results of the Study in Adults with Treatment-Resistant Depression

In the Phase 3 study of adults with treatment-resistant depression, patients were randomized to flexibly dosed esketamine nasal spray (56 or 84 mg) added to a newly initiated oral antidepressant or placebo nasal spray added to a newly initiated oral antidepressant.

Primary Efficacy Endpoint

The primary efficacy endpoint, change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, demonstrated the statistically significant clinical improvement in patients’ depressive symptoms for esketamine nasal spray plus an oral antidepressant at day 28 (Least Squares Mean Difference Standard Error [SE] from placebo nasal spray plus a newly initiated oral AD: -4.0 [1.69], 95% Confidence Interval: -7.31, -0.64; one-sided p=0.01).

Secondary and Other Efficacy Endpoints

The first key secondary endpoint (onset of clinical response by 24 hours post-dose that is sustained through day 28) numerically favored esketamine nasal spray plus an oral antidepressant vs. placebo nasal spray plus an oral antidepressant, but did not meet statistical significance. The other two key secondary endpoints (Sheehan Disability Scale [SDS], a patient-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) could not be formally evaluated since onset of clinical response was not statistically significant. Among other endpoints, response rate was also notable with 69.3% responding in the esketamine group vs. 52.0% in the nasal spray placebo group at 28 days (response is defined as $\geq 50\%$ improvement in MADRS from baseline). Remission rate (defined as a MADRS total score ≤ 12) at day 28 was 52.5% (53/101) and 31.0% (31/100) for the esketamine and nasal spray placebo groups, respectively.

The most common treatment-emergent adverse events reported ($>10\%$ of patients) in the esketamine group were metallic taste, nausea, vertigo, dizziness, headache, drowsiness, short lived perceptual changes, blurred vision, paraesthesia (tingling sensation) and anxiety.

The most common treatment-emergent adverse events (>10% of patients) reported in the placebo group were metallic taste and headache.

For further information about this study, visit the [ClinicalTrials.gov](https://clinicaltrials.gov) website.

Results of the Study in Elderly Patients with Treatment-Resistant Depression

Janssen conducted a separate Phase 3 study in elderly patients with treatment-resistant depression. Elderly populations with major depressive disorder are historically hard to treat and often have co-morbidities and long-standing depression. To improve tolerability, patients were given a lower starting dose of esketamine nasal spray (28 mg) alongside a newly initiated oral antidepressant followed by flexibly dosed 28 mg, 56 mg or 84 mg esketamine nasal spray. In the comparator arm patients were given placebo nasal spray alongside a newly initiated oral antidepressant.

Primary Efficacy Endpoint

Although statistical significance for the primary endpoint for the overall patient population studied was narrowly missed, results favored the esketamine nasal spray plus a newly initiated oral antidepressant group (median unbiased estimate of the difference from placebo nasal spray plus a newly initiated oral antidepressant: -3.6, 95% Confidence Interval: -7.20, 0.07; one-sided p=0.029). To put this into context, an analysis of placebo-controlled data from three prior studies conducted by Duru and Fantino determined that the minimum clinically important difference from placebo in MADRS of 1.9 or higher was clinically meaningful.⁴

Safety results were consistent with previous studies of esketamine in younger adult populations. The most common treatment-emergent adverse events reported (>10% of patients) in the esketamine group were dizziness, nausea, headache, fatigue, increased blood pressure, vertigo and short lived perceptual changes. There were no treatment-emergent adverse events reported in >10% of patients in the placebo group.

Esketamine nasal spray has an acceptable safety and tolerability profile, based on the adverse event data from both Phase 3 studies. Adverse events and associated symptoms were seen predominantly on the day of dosing and were generally transient and resolved on the day of dosing.

These findings represent two of the five Phase 3 studies that comprise Janssen's treatment-resistant depression program with esketamine nasal spray. The results from these studies will inform regulatory filings for esketamine nasal spray in treatment-resistant depression, for which Janssen has received Breakthrough Therapy designation from the U.S. Food and Drug Administration (FDA). Data from other Phase 3 studies will be presented later in 2018.

For further information about this study, visit the [ClinicalTrials.gov](https://clinicaltrials.gov) website.

About the Studies

In both Phase 3 studies, esketamine or placebo was provided in single-use disposable nasal spray devices containing 200 µl of solution (i.e., two sprays), and administered under the supervision of a health care professional. A bittering agent was added to placebo to simulate the taste of esketamine, to help mask the treatment assignment.

The study in adults with treatment-resistant depression was a Phase 3, double-blind, active-control, flexibly dosed, multi-center study using blinded raters, conducted at 39 sites in

Spain, Germany, Czech Republic, Poland, and the United States from August 2015 to November 2017. The study enrolled adults with moderate-to-severe, non-psychotic, recurrent or persistent depression, and history of non-response to ≥ 2 antidepressants in the current episode of depression, with one of them assessed prospectively. Non-responders were randomized (1:1) to flexibly-dosed esketamine nasal spray (56 or 84 mg twice weekly) plus a newly initiated oral antidepressant (N=114) or placebo nasal spray plus a newly initiated oral antidepressant (N=109). The primary efficacy endpoint – change from baseline to day 28 in MADRS total score – was assessed among patients who received ≥ 1 dose of (nasal spray and oral) study medication by mixed-effects model using repeated measures (MMRM) using a one-sided significance level of 0.025. In this study, 435 patients were screened, 227 randomized, and 197 completed the double-blind phase. The mean [Standard Deviation – SD] baseline MADRS total score was 37.1 [5.67].

The study in elderly patients with treatment-resistant depression was a Phase 3, double-blind, active-controlled, flexibly dosed, multi-center study. Patients ≥ 65 years of age were randomized 1:1 to either esketamine nasal spray plus a new oral antidepressant (N=72) or placebo nasal spray plus a new oral antidepressant (N=66). The primary endpoint was the change in the MADRS total score from day 1 (baseline) to day 28. Statistical analysis employed mixed-effects model repeated measures (MMRM), with a weighted combination test to account for an interim analysis for sample size re-estimation, using a one-sided significance level of 0.025. In this study, 302 patients were screened, 138 randomized, and 122 completed the double-blind phase. The mean [SD] patient age was 70.0 [4.52] years and mean baseline MADRS total score was 35.2 [6.16].

About Esketamine

Esketamine nasal spray 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, also known as a glutamate receptor modulator, which is thought to help restore synaptic connections in brain cells in people with major depressive disorder - a novel mechanism of action, meaning it works differently than currently available therapies for depression.

Esketamine received two 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.⁵ If approved by regulatory authorities, esketamine would be one of the first new approaches to treat refractory major depressive disorder available to patients in the last 50 years.

About Major Depressive Disorder

Major depressive disorder affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide.⁶ 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.⁶ 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.⁷

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/emea. Follow us at www.twitter.com/JanssenEMEA.

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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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