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Janssen Phase 3 Study Programme of Esketamine Nasal Spray in Patients with Treatment-Resistant Depression Presented for the First Time in Europe

One long-term study provides evidence that esketamine delayed time to relapse
A second study shows esketamine was generally well tolerated with no new safety signals

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BEERSE, Belgium--(BUSINESS WIRE)--The Janssen Pharmaceutical Companies of Johnson & Johnson presented for the first time in Europe data from pivotal Phase 3 clinical studies of the investigational compound esketamine nasal spray in treatment-resistant depression.[1,2,3,4] The studies, conducted by Janssen Research & Development, LLC, were presented at the 31st International College of Neuropsychopharmacology (CINP) congress in Vienna, Austria.

Data discussed from the Phase 3 programme included results from the maintenance phase of a long-term relapse prevention study in adults with treatment-resistant depression. The data found that continuing treatment with esketamine nasal spray plus an oral antidepressant in patients beyond 16 weeks showed clinically meaningful and statistically significant superiority to treatment with an oral antidepressant plus placebo nasal spray in delaying time to relapse of symptoms of depression. Furthermore, the

data indicated that patients in stable remission treated with esketamine nasal spray plus an oral antidepressant reduced the risk of relapse by 51% (estimated Hazard Ratio = 0.49; 95% CI: 0.29, 0.84) compared to patients in the oral antidepressant plus placebo nasal spray group. The five most frequently reported adverse events in the esketamine-treated patients (≥5%) during the maintenance phase were temporary impaired sense of taste, vertigo, dissociation, drowsiness, and dizziness.[1]

A long-term safety study of esketamine nasal spray showed that in adults with treatment-resistant depression, esketamine nasal spray plus an oral antidepressant was generally well tolerated with no new safety signals identified after repeated long-term dosing for up to one-year (52 weeks). The safety profile of esketamine was similar to that observed in previous short-term Phase 2 and 3 studies in patients with treatment-resistant depression. The data from this open-label study also indicated that treatment with esketamine nasal spray plus an oral antidepressant appeared to be associated with sustained improvement in depressive symptoms for up to 52 weeks. The most common treatment-emergent adverse events (≥10% patients) were dizziness, dissociation, nausea, headache, drowsiness, temporary impaired sense of taste, diminished oral sense of touch or sensation, vertigo, vomiting, and viral upper respiratory tract infection.[2]

“Major Depressive Disorder affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide,[5]therefore it is important we continue to study and report the results of these studies in this area,” said Professor Siegfried Kasper, Head of the Department of Psychiatry and Psychotherapy at the Medical University of Vienna, Austria. “These data provide insights related to the safety of esketamine in patients with treatment-resistant depression over the long-term and show that esketamine may be beneficial in terms of extending time to relapse in a patient population that is challenging to treat.”

Two additional esketamine short-term randomised, double blind, active-controlled studies, one in adults and one in in patients aged 65 years or over, were also presented at CINP.[3,4]

In the first study in adults with treatment-resistant depression, 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. This study showed that treatment with esketamine plus an antidepressant achieved superiority versus an active comparator, which is considered clinically meaningful, especially in patients deemed to be treatment-resistant. The most common treatment-emergent adverse events reported (>10% of patients) in the esketamine group were temporary impaired sense of taste, nausea, vertigo, dizziness, headache, drowsiness, short lived perceptual changes, blurred vision, paresthesia (tingling sensation) and anxiety. The most common treatment-emergent adverse events (>10% of patients) reported in the oral

antidepressant plus placebo group were temporary impaired sense of taste and headache.[3]

In a second study in elderly patients aged 65 years or older with treatment-resistant depression – a patient cohort that is historically hard to treat – treatment with flexibly dosed esketamine plus a newly initiated oral antidepressant demonstrated a clinically meaningful effect compared to a newly initiated oral antidepressant plus placebo nasal spray, although statistical significance was not reached. Esketamine was generally well tolerated in the study. 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 dissociative and perceptual changes. There were no treatment-emergent adverse events reported in >10% of patients in the oral antidepressant and placebo group.[4]

“We are pleased to share these results from our Phase 3 program for esketamine nasal spray. They reinforce its potential to help patients who haven’t responded to available therapies,” said Mathai Mammen, M.D, Ph.D., Global Head, Janssen Research & Development, LLC. “We look forward to submitting all results from our esketamine treatment-resistant depression studies to regulatory authorities, with a view to bringing a new treatment option to people in need.”

Results of the Relapse Prevention Study[1]

This was a Phase 3, randomised, double-blind, multi-center study, in which 705 adult patients were directly enrolled or transferred from one of two other short-term esketamine Phase 3 studies. The study consisted of four phases: Screening phase (4 weeks); Open-label Induction phase (4 weeks); Maintenance phase (48 weeks); Follow-up phase (4 weeks).

After initial treatment for 16 weeks with esketamine plus an oral antidepressant, patients who were stable remitters were randomised to either continue with esketamine nasal spray (56 mg or 84 mg) plus an oral antidepressant or were switched to an oral antidepressant plus placebo nasal spray with repeated, intermittent dosing. Stable, or sustained, remission criteria were met when a patient achieved a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≤12 in at least three of the four weekly assessments conducted during weeks 12–16 of the initial 16-week treatment phase. Relapse criteria used in the maintenance phase of the study were met when a patient had a MADRS total score of ≥22 for two consecutive weeks or was hospitalised for worsening depression or had a clinically relevant event indicative of relapse.

Remission is clinically defined as virtually complete relief of symptoms, generally accompanied by improvement in functioning across a variety of areas.[6] Relapse is

clinically defined as having symptoms that return after improvement of depression and which meet Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for depression.[7]

Primary Efficacy Endpoint

The primary efficacy endpoint was time to relapse among patients who were in stable remission after 16 weeks of treatment with esketamine nasal spray plus an oral antidepressant and who were randomised to continue treatment with esketamine plus an oral antidepressant or who stopped esketamine and were switched to placebo nasal spray, while continuing the oral antidepressant. The results significantly favoured continued treatment with esketamine nasal spray plus an oral antidepressant in delaying relapse compared to an oral antidepressant plus placebo nasal spray. Overall, among stable remitters, 24 (26.7%) patients in the esketamine plus an oral antidepressant group and 39 (45.3%) patients in the oral antidepressant plus placebo nasal spray group experienced a relapse event during the maintenance phase. The estimated hazard ratio of esketamine nasal spray plus an oral antidepressant relative to an oral antidepressant plus placebo nasal spray based on the Cox proportional hazards model was 0.49 (95% Confidence Interval:0.29, 0.84), indicating that patients treated with esketamine plus an oral antidepressant had a 51% reduced risk of relapse. Based on a weighted combination log-rank test, the difference between groups for the time to relapse was clinically and statistically significant (two-sided p=0.003).

Secondary Efficacy Endpoint

Recognising the clinical importance of response in patients with treatment-resistant depression, a second group of patients were also studied in the maintenance phase of this study. These were patients who had met criteria for stable response (i.e. ≥ 50% improvement from baseline for the last 2 weeks of the initial 16-week treatment phase), but who did not meet criteria for stable remission. For the secondary efficacy endpoint, time to relapse among patients with stable response (but without remission), 16 (25.8%) patients in the esketamine nasal spray plus an oral antidepressant group and 34 (57.6%) patients in the oral antidepressant plus placebo nasal spray group relapsed. The estimated hazard ratio of esketamine nasal spray plus an oral antidepressant relative to an oral antidepressant plus placebo nasal spray based on the Cox proportional hazards model was 0.30 (95% Confidence Interval: 0.16, 0.55), indicating that patients treated with esketamine plus an oral antidepressant had a 70% reduced risk of relapse. The difference between treatment groups for the time to relapse was clinically and statistically significant (p<0.001) using a two-sided log-rank test.

Safety Results

Safety results were consistent with previous findings from completed Phase 2 and 3 studies of esketamine nasal spray. The most common adverse events (>10%) reported in the esketamine group during the maintenance phase were temporary impaired sense

of taste (27.0%), vertigo (25.0%), dissociation (22.4%), drowsiness (21.1%), dizziness (20.4%), headache (17.8%), nausea (16.4%), vision blurred (15.8%) and oral hypoesthesia (diminished sense of touch or sensation) (13.2%). Adverse events and associated symptoms were seen predominantly on the day of dosing, were generally transient, mild or moderate in severity, and resolved on the day of dosing. There were no adverse events reported in ≥10% of patients in the oral antidepressant and placebo nasal spray group. No deaths were reported.

Results of the Long-term Safety Study[2]

This was a Phase 3, open-label, safety study, in which 802 adult patients (≥18 years) were directly enrolled or transferred from another Phase 3 study of elderly (≥65 years) patients. The study consisted of four phases: Screening phase (4 weeks); Open-label Induction phase (4 weeks); Maintenance phase (48 weeks); Follow-up phase (4 weeks). Patients received esketamine nasal spray (28 mg in elderly patients only, 56 mg or 84 mg) plus an oral antidepressant with repeated, intermittent dosing for up to one year. Patients' safety and depressive symptoms were assessed and monitored throughout the study.

Primary Safety Endpoints

The most common treatment-emergent adverse events during the treatment phases (≥10% patients) were dizziness (32.9%), dissociation (27.4%), nausea (25.1%), headache (24.9%), drowsiness (16.7%), temporary impaired sense of taste and hypoesthesia (diminished sense of touch or sensation) (11.8% each), vertigo (11.0%), vomiting (10.8%), and viral upper respiratory tract infection (10.2%). Fifty-five (6.9%) patients experienced 68 serious treatment-emergent adverse events. Of these, five serious treatment-emergent adverse events from four subjects were assessed by the investigator as esketamine nasal spray-related. There were two deaths which the investigator determined to be unrelated to esketamine nasal spray or oral antidepressant use. Laboratory tests, physical examination, and nasal tolerability revealed no trends of clinical concern in patients treated with esketamine nasal spray for up to 52 weeks. No clinically meaningful changes in cognition were found. No cases of interstitial or ulcerative cystitis were reported.

Secondary Efficacy Endpoints

Due to its open label design, this study was not intended to formally evaluate the efficacy of esketamine. However, esketamine nasal spray appeared to sustain improvement in depressive symptoms for up to 52 weeks in patients with treatment-resistant depression. The mean change in MADRS total score from the induction baseline to the four-week endpoint was -16.4 (8.76) and from the subsequent maintenance baseline to endpoint was 0.3 (8.12). At the induction phase endpoint (day 28), the response rate (percentage of patients with ≥50% reduction in the MADRS total score) was 78.4% and the remission rate (percentage of patients with MADRS total

score ≤12) was 47.2%. Of those who responded to treatment and proceeded to the maintenance phase, 76.5% were responders and 58.2% were remitters at the 52-week endpoint.

Results of the Short-term Study in Adults with Treatment-Resistant Depression[3]

In the Phase 3 study of adults with treatment-resistant depression, patients were randomised 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 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 favoured esketamine nasal spray plus an oral antidepressant vs. placebo nasal spray plus an oral antidepressant, but did not meet statistical significance. Response rate was notable with 69.3% (70/101) responding in the esketamine group vs. 52.0% (52/100) in the oral antidepressant and nasal spray placebo group at 28 days (response is defined as ≥ 50% improvement in MADRS score 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 plus oral antidepressant and oral antidepressant plus nasal spray placebo groups, respectively.

Safety Results

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

Results of the Short-term Study in Elderly Patients with Treatment-Resistant Depression[4]

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 favoured the esketamine nasal spray plus a newly initiated oral antidepressant group (median unbiased estimate of the difference in MADRS score from baseline to day 28 compared with 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 average 2-point difference from placebo has frequently been used to establish a clinically meaningful difference on the MADRS score for an antidepressant.

Safety Results

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.

For further information about these studies, visit the ClinicalTrials.gov website.

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.[8]

About Major Depressive Disorder

Major depressive disorder affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide.[5]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.[5] Although currently available antidepressants are effective for many patients, about one third of patients do not respond to treatment and are considered to have treatment-resistant depression.[9]

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 http://www.janssen.com/emea. Follow us at www.twitter.com/JanssenEMEA. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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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 and treatment impact 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, any of the other Janssen Pharmaceutical Companies of Johnson & Johnson 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; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns 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 the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's subsequent Quarterly Reports on Form 10-Q and other 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 nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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