News Release

Media Contact:
Stela Meirelles
+1 732-258-1540 (mobile)

Investor Contacts:
Christopher DelOrefice
+1 732-524-2955 (office)

Lesley Fishman
+1 732-524-3922 (office)

Janssen Submits Supplemental New Drug Application to U.S. FDA for SPRAVATO® (esketamine) CIII Nasal Spray for the Rapid Reduction of Depressive Symptoms in Adults with Major Depressive Disorder Who Have Active Suicidal Ideation with Intent

If approved, SPRAVATO® would be the first treatment for this severely ill population[1] who historically have been excluded from antidepressant clinical trials

Submission is based on data from the ASPIRE I & II trials evaluating the efficacy and safety of SPRAVATO® in adults with major depressive disorder who have active suicidal ideation with intent

TITUSVILLE, NJ, OCTOBER 2, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) seeking a new indication for SPRAVATO® (esketamine) CIII nasal spray for the rapid reduction of depressive symptoms in adult patients with major depressive disorder (MDD) who have active suicidal ideation with intent. The submission is based on results from the Phase 3 ASPIRE I & II trials, which evaluated the efficacy and safety of SPRAVATO® versus placebo nasal spray in this high-risk patient population when used in addition to comprehensive standard of care (SOC). In these studies, comprehensive SOC included initial hospitalization and newly initiated and/or optimized antidepressant therapy.[2,3,4]

"This submission is a significant step in helping a vulnerable patient population by providing a potential treatment option to rapidly reduce symptoms of depression in adults with active suicidal ideation with intent, which constitutes a psychiatric emergency that requires immediate intervention," said Husseini K. Manji, M.D., Global Head, Neuroscience

Therapeutic Area, Janssen Research & Development, LLC. "It extends our focus on severe manifestations of major depressive disorder beyond the current indication for treatment-resistant depression."

The data from the ASPIRE I & II trials were recently presented at the 32nd European College of Neuropsychopharmacology (ECNP), which took place September 7-10 in Copenhagen, Denmark. The double-blind, randomized, placebo-controlled, multicenter studies both met their respective primary efficacy endpoint, which was a reduction in depressive symptoms at 24 hours after the first dose, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS). In both studies, SPRAVATO® 84 mg plus SOC showed clinically meaningful and statistically significant superiority (p=0.006) compared to placebo plus SOC in rapidly reducing symptoms of major depressive disorder. In these studies, comprehensive SOC included initial hospitalization and newly initiated and/or optimized antidepressant therapy.[2,3,4]

The treatment difference between the two groups on the secondary endpoint of suicidality was not statistically significant. In the studies both SPRAVATO® plus comprehensive SOC and placebo plus comprehensive SOC resulted in improvement in severity of suicidality (a composite endpoint including suicidal ideation and behavior) as measured by the revised Clinical Global Impression of Severity of Suicidality (CGI-SS-R) at 24 hours after the first dose. This may be due to the substantial beneficial effects of comprehensive SOC utilized in the clinical trial, including the immediate impact of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis in patients in both treatment groups.[2,3,4]

The FDA granted Breakthrough Therapy designation to esketamine nasal spray for major depressive disorder with imminent risk for suicide in August 2016[5] and approved SPRAVATO® (esketamine) CIII nasal spray, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults on March 5, 2019.[6]

About the ASPIRE I & II Trials

At 24 hours after the first dose of study medication in ASPIRE I & II, the mean difference observed in the reduction of depressive symptoms between the SPRAVATO® plus SOC group and the placebo plus SOC group was 3.8 points and 3.9 points, respectively, as measured by the MADRS total score.[2,3,4]

The effect of SPRAVATO® plus SOC on symptoms of major depressive disorder was apparent at four hours after the first dose. Between four hours and 25 days, both the SPRAVATO®

and placebo groups continued to improve, and the magnitude of difference between the groups generally remained throughout the 25-day double-blind period. In the ASPIRE I & II trials, 54 percent and 47 percent, respectively, of the SPRAVATO® plus SOC group achieved remission (MADRS score ≤ 12) by the end of the double-blind period. The clinical improvement during the double-blind period was maintained over the nine-week follow-up period in both treatment groups, during which time the ongoing oral antidepressant was continued.[2,3,4]

In the ASPIRE I & II trials, SPRAVATO® plus SOC was well-tolerated with no new safety signals.[2,3,4] The safety profile observed was consistent across the two Phase 3 studies in patients with major depressive disorder who have active suicidal ideation with intent and with previous studies of SPRAVATO® in patients with treatment-resistant depression.[6] In the clinical trials, the most common side effects of SPRAVATO® plus SOC were dizziness, dissociation, nausea, somnolence, blurred vision, vomiting, paresthesia, increased blood pressure and sedation.[2,3,4]

About SPRAVATO®

SPRAVATO® is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor – an ionotropic glutamate receptor. It has a novel mechanism of action, meaning it works differently than currently available therapies for major depressive disorder.[6,9,10,11,12,13]

SPRAVATO® (esketamine) CIII nasal spray is approved in the United States for use in conjunction with an oral antidepressant in adults with treatment-resistant depression (TRD) and has been submitted for health authorities' review for TRD in other markets around the world, including Europe.[6,14] The FDA granted Breakthrough Therapy designation to esketamine nasal spray for treatment-resistant depression in November 2013 and for major depressive disorder with imminent risk for suicide in August 2016.[5]

About Major Depressive Disorder in Adult Patients Who Have Active Suicidal Ideation with Intent

Major depressive disorder (MDD) affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide.[15] With approximately 17 million adults diagnosed in the U.S., people with MDD experience suffering from a serious, biologically-based disease that has a significant negative impact on all aspects of life, including quality of life and function.[16,17]

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

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

What is SPRAVATO®?

SPRAVATO® is a prescription medicine, used along with an antidepressant taken by mouth, for treatment-resistant depression (TRD) in adults.

SPRAVATO® is not for use as a medicine to prevent or relieve pain (anesthetic). It is not known if SPRAVATO® is safe or effective as an anesthetic medicine.

It is not known if SPRAVATO® is safe and effective in children.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about SPRAVATO®?

SPRAVATO® can cause serious side effects, including:

- **Sedation and dissociation**. SPRAVATO® may cause sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, your thoughts, feelings, space and time (dissociation).
    - Tell your healthcare provider right away if you feel like you cannot stay awake or if you feel like you are going to pass out.
    - Your healthcare provider must monitor you for serious side effects for at least 2 hours after taking SPRAVATO®. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Abuse and misuse.** There is a risk for abuse and physical and psychological dependence with SPRAVATO® treatment. Your healthcare provider should check you for signs of abuse and dependence before and during treatment with SPRAVATO®.
    - Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
    - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS).** Because of the risks for sedation, dissociation, and abuse and misuse, SPRAVATO® is only available through a restricted program called the SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS) Program. SPRAVATO® can only be administered at healthcare settings certified in the SPRAVATO® REMS Program and to patients enrolled in the program.
- **Increased risk of suicidal thoughts or actions.** SPRAVATO® may cause worsening of depression and suicidal thoughts and behaviors, especially during the first few months of treatment and when the dose is changed. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a higher risk of

having suicidal thoughts or actions. These include people who have (or have a family history of) depression or a history of suicidal thoughts or actions.

- **How can I watch for and try to prevent suicidal thoughts and actions?**
  - Pay close attention to any changes, especially sudden changes, in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.
- **Tell your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:**
  - attempts to commit suicide
  - thoughts about suicide or dying
  - worsening depression
  - other unusual changes in behavior or mood

SPRAVATO® is not for use in children.

Do not take SPRAVATO® if you:

- have blood vessel (aneurysmal vascular) disease (including in the brain, chest, abdominal aorta, arms and legs)
- have an abnormal connection between your veins and arteries (arteriovenous malformation)
- have a history of bleeding in the brain
- are allergic to esketamine, ketamine, or any of the other ingredients in SPRAVATO®.

If you are not sure if you have any of the above conditions, talk to your healthcare provider before taking SPRAVATO®.

Before you take SPRAVATO®, tell your healthcare provider about all of your medical conditions, including if you:

- have heart or brain problems, including:
  - high blood pressure (hypertension)
  - slow or fast heartbeats that cause shortness of breath, chest pain, lightheadedness, or fainting
  - history of heart attack
  - history of stroke
  - heart valve disease or heart failure
  - history of brain injury or any condition where there is increased pressure in the brain
- have liver problems
- have ever had a condition called "psychosis" (see, feel, or hear things that are not there, or believe in things that are not true).
- are pregnant or plan to become pregnant. SPRAVATO® may harm your baby. You should not take SPRAVATO® if you are pregnant.
  - Tell your healthcare provider right away if you become pregnant during treatment with SPRAVATO®.
  - If you are able to become pregnant, talk to your healthcare provider about methods to prevent pregnancy during treatment with SPRAVATO®.
  - There is a pregnancy registry for women who are exposed to SPRAVATO® during pregnancy. The purpose of the registry is to collect information about the health of women exposed to SPRAVATO® and their baby. If you become pregnant during treatment with SPRAVATO®, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.
- are breastfeeding or plan to breastfeed. You should not breastfeed during treatment with SPRAVATO®.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking SPRAVATO® with certain

medicine may cause side effects. Especially tell your healthcare provider if you take Central Nervous System (CNS) depressants, psychostimulants, or Monoamine oxidase inhibitors (MAOIs) medicines.

How will I take SPRAVATO®?

- You will take SPRAVATO® nasal spray yourself, under the supervision of a healthcare provider in a healthcare setting. Your healthcare provider will show you how to use the SPRAVATO® nasal spray device.
- Your healthcare provider will tell you how much SPRAVATO® you will take and when you will take it.
- Follow your SPRAVATO® treatment schedule exactly as your healthcare provider tells you to.
- During and after each use of the SPRAVATO® nasal spray device, you will be checked by a healthcare provider who will decide when you are ready to leave the healthcare setting.
- You will need to plan for a caregiver or family member to drive you home after taking SPRAVATO®.
- If you miss a SPRAVATO® treatment, your healthcare provider may change your dose and treatment schedule.
- Some people taking SPRAVATO® get nausea and vomiting. You should not eat for at least 2 hours before taking SPRAVATO® and not drink liquids at least 30 minutes before taking SPRAVATO®.
- If you take a nasal corticosteroid or nasal decongestant medicine take these medicines at least 1 hour before taking SPRAVATO®.

What should I avoid while taking SPRAVATO®?
Do not drive, operate machinery, or do anything where you need to be completely alert after taking SPRAVATO®. **Do not** take part in these activities until the next day following a restful sleep. See **"What is the most important information I should know about SPRAVATO®?"**

What are the possible side effects of SPRAVATO®?
SPRAVATO® may cause serious side effects including:

- See "**What is the most important information I should know about SPRAVATO®?**"
- **Increased blood pressure.** SPRAVATO® can cause a temporary increase in your blood pressure that may last for about 4 hours after taking a dose. Your healthcare provider will check your blood pressure before taking SPRAVATO® and for at least 2 hours after you take SPRAVATO®. Tell your healthcare provider right away if you get chest pain, shortness of breath, sudden severe headache, change in vision, or seizures after taking SPRAVATO®.
- **Problems with thinking clearly.** Tell your healthcare provider if you have problems thinking or remembering.
- **Bladder problems.** Tell your healthcare provider if you develop trouble urinating, such as a frequent or urgent need to urinate, pain when urinating, or urinating frequently at night.

The most common side effects of SPRAVATO® when used along with an antidepressant taken by mouth include: dissociation, dizziness, nausea, sedation, spinning sensation, reduced sense of touch and sensation, anxiety, lack of energy, increased blood pressure, vomiting, and feeling drunk.

If these common side effects occur, they usually happen right after taking SPRAVATO® and go away the same day.

These are not all the possible side effects of SPRAVATO®.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal.

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, any of the other Janssen Pharmaceutical Companies 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; manufacturing difficulties and delays; 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 descriptions 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 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, 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. Neither 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.

###

1. Melander H, Salmonson T, Abadie E, et al: A regulatory Apologia--A review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *Eur Neuropsychopharmacol* 2008;18(9):623-627.
2. Carla Canuso, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: new data from a global registration program. Presented at European College of Neuropsychopharmacology (ECNP) congress; September 2019; Copenhagen, Denmark.
3. Dong-Jing Fu, Carla Canuso, Dawn Ionescu, Xiang Li, Rosanne Lane, Pilar Lim, David Hough, Wayne Drevets, Husseini Manji. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: ASPIRE-1 study. Presented at European College of Neuropsychopharmacology (ECNP) congress; September 2019; Copenhagen, Denmark.
4. Dawn Ionescu, Carla Canuso, Dong-Jing Fu, Xin Qiu, Rosanne Lane, Pilar Lim, David Hough, Wayne Drevets, Husseini Manji. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: ASPIRE-2 study. Presented at European College of Neuropsychopharmacology (ECNP) congress; September 2019; Copenhagen, Denmark.
5. 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 August 2019.

6. SPRAVATO® [Prescribing Information]. Titusville, N.J., Janssen Pharmaceuticals, Inc.
7. Montgomery SA, Moller HJ: Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? *Int Clin Psychopharmacol* 2009;24(3):111-118.
8. Melander H, Salmonson T, Abadie E, et al: A regulatory Apologia--A review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *Eur Neuropsychopharmacol* 2008;18(9):623-627.
9. 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.
10. 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: American Society of Clinical Psychopharmacology; May 2018; Miami, Florida.
11. E Wajs, L Aluisio, R Morrison, EJ Daly, R Lane, P Lim, R Holder, G Sanacora, AH Young, S Kasper, AH Sulaiman, C Li, J Paik, H Manji, D Hough, WC Drevets, JB Singh. Long-Term Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Patients with Treatment-Resistant Depression: Phase 3, Open Label Safety and Efficacy Study (SUSTAIN-2). Poster presented at: The American Society of Clinical Psychopharmacology Meeting; May 2018; Miami, Florida.
12. M Fedgchin, M Trivedi, EJ Daly, R Melkote, R Lane, P Lim, D Vitagliano, P Blier, M Fava, M Liebowitz, A Ravindran, R Gaillard, H Ameele, H Manji, D Hough, WC Drevets, JB Singh. Randomized, Double-Blind Study of Fixed-Dosed Intranasal Esketamine Plus Oral Antidepressant vs. Active Control in Treatment-Resistant Depression. Poster presented at: 9th Biennial Conference of the International Society for Affective Disorders (ISAD) and the Houston Mood Disorders Conference; September 2018; Houston, TX.
13. Rachel Ochs-Ross, M.D., Ella J. Daly, MD, Yun Zhang, Ph.D., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Karen Foster, B.S., David Hough, M.D., Husseini Manji, M.D., Wayne C. Drevets, M.D., Gerard Sanacora, M.D., Ph.D., Caleb Adler, M.D., Rupert McShane, M.D., Raphaël Gaillard, M.D., Ph.D., Jaskaran B. Singh, M.D. Efficacy and safety of intranasal esketamine plus an oral antidepressant in elderly patients with treatment-resistant depression. Poster presented at: American Psychiatric Association (APA) Annual Meeting; May 2018; New York, NY.
14. Janssen Press Release. Janssen Announces U.S. FDA Approval of SPRAVATO® (esketamine) CIII Nasal Spray for Adults with Treatment-Resistant Depression (TRD) Who Have Cycled Through Multiple Treatments Without Relief. Available at: https://www.janssen.com/janssen-announces-us-fda-approval-SPRAVATO®-esketamine-ciii-nasal-spray-adults-treatment-resistant. Accessed March 2019.
15. World Health Organization. Depression. Available at: http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed June 2018.
16. National Institute of Mental Health. Major depression among adults. https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml. Accessed May 16, 2019.
17. Hofmann S et al. Cogn Behav Ther. 2017;46(4):265–286