European Union Risk Management Plan
SPRAVATO (Esketamine Nasal Spray)

Data lock point for current RMP	03 April 2023	Version number	6.2

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QPPV Name:	Dr. Laurence OSTER-GOZET PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	6.2
Rationale for submitting an updated RMP	• Completion of the category 3 additional pharmacovigilance activity 54135419TRD3008: An open-label long-term extension safety study of intranasal esketamine in TRD. • Removal of the important potential risks of cognitive disorders and memory impairment (long-term use) and interstitial cystitis (long-term use).
Summary of significant changes in this RMP	Safety Concerns: • Part II Module SV: Populated with postmarketing exposure data. • Part II Module SVII: Removed the important potential risks of cognitive disorders and memory impairment (long-term use) and interstitial cystitis (long-term use). Pharmacovigilance Plan: • Part III: Removed 54135419TRD3008 as a category 3 additional pharmacovigilance activity due to its completion.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
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Details of the Currently Approved RMP:

Version number of last agreed RMP:	5.2
Approved within procedure	EMEA/H/C/004535/II/0021
Date of approval (opinion date)	08 February 2024

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	esketamine hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Psychoanaleptics; Other antidepressants, ATC code: N06AX27
MAH	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	SPRAVATO®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class** Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive antagonist of the NMDAR, an ionotropic glutamate receptor.
	Summary of mode of action Through NMDAR antagonism, esketamine produces a transient increase in glutamate release, leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor stimulation and subsequently to increases in neurotrophic signaling, which may contribute to the restoration of the synaptic function in brain regions involved with the regulation of mood and emotional behavior. Restoration of dopaminergic neurotransmission in brain regions involved in reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.
	Important information about its composition: Not applicable.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	**Current:** <u>TRD:</u> SPRAVATO, in combination with a SSRI or SNRI, is indicated for adults with TRD who have not responded to at least two different treatments with ADs in the current moderate to severe depressive episode.
	<u>Acute short-term treatment of psychiatric emergency due to MDD:</u> SPRAVATO, co-administered with oral AD therapy, is indicated in adults with a moderate to severe episode of MDD, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency. **Proposed:** Not applicable.

Dosage in the EEA

Current:

TRD:

SPRAVATO is for nasal use only. The nasal spray device is a single-use device that delivers a total of 28 mg of esketamine, in 2 sprays (1 spray per nostril). To prevent loss of medicinal product, the device should not be primed before use. SPRAVATO is intended for administration by the patient under the direct supervision of an HCP, using 1 device (for a 28 mg dose), 2 devices (for a 56 mg dose), or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device.

The dosage recommendations for TRD are shown below. It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the maintenance phase, SPRAVATO dosing should be individualized to the lowest frequency to maintain remission/response.

Recommended Dosing in Adults <65 Years with TRD	
Induction Phase	**Maintenance Phase**
Weeks 1-4: Starting day 1 dose: 56 mg Subsequent doses: 56 mg or 84 mg twice a week	**Weeks 5-8:** 56 mg or 84 mg once weekly **From Week 9**: 56 mg or 84 mg every 2 weeks or once weekly
Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine the need for continued treatment.	The need for continued treatment should be reexamined periodically.

Recommended Dosing in Adults ≥65 Years with TRD	
Induction Phase	**Maintenance Phase**
Weeks 1-4: Starting day 1 dose: 28 mg Subsequent doses: 28 mg, 56 mg, or 84 mg twice a week; all dose changes should be in 28-mg increments	**Weeks 5-8:** 28 mg, 56 mg, or 84 mg once weekly; all dose changes should be in 28-mg increments **From Week 9**: 28 mg, 56 mg, or 84 mg every 2 weeks or once weekly; all dose changes should be in 28-mg increments
Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine the need for continued treatment.	The need for continued treatment should be reexamined periodically.

After depressive symptoms improve, treatment is recommended for at least 6 months.

Acute short-term treatment of psychiatric emergency due to MDD:

The recommended dosage of SPRAVATO for acute short-term treatment of psychiatric emergency due to MDD in adult patients (<65 years) is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made based on tolerability. After 4 weeks of treatment with SPRAVATO, the oral AD therapy should be continued, per clinical judgement.

	In these patients, treatment with SPRAVATO should be part of the comprehensive clinical care plan. **Proposed:** Not applicable.
Pharmaceutical form(s) and strengths	**Current:** Nasal spray, solution. Clear, colorless, aqueous solution. Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.
	Proposed: Not applicable.

Is/will the product be subject of additional monitoring in the EU?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

TRD

MDD is a common and serious psychiatric disorder affecting over 30 million individuals in the EU (Wittchen 2011). MDD is the leading cause of disability (measured as years lived with disability) worldwide and is associated with elevated mortality and suicide risk (Global Burden of Disease Study 2017; Walker 2015; World Health Organization 2018). About 30% of patients with MDD fail to achieve remission from their depressive symptoms despite treatment with multiple medications (Fava 2003; Rush 2006); these patients are identified as suffering from TRD. A globally accepted definition for TRD does not yet exist. The EMA defines TRD as lack of clinically meaningful improvement despite the use of adequate doses of at least two AD agents, derived from the group(s) of commonly used first line treatment, prescribed for adequate duration with adequate affirmation of treatment adherence (EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression 2013). However, a variety of definitions have been used in studies ranging from nonresponse to 1 AD for ≤4 weeks to a failure to respond to multiple adequate (duration and dosage) trials of different classes of ADs and electroconvulsive therapy (Schosser 2012). This variation in definitions makes it difficult to compare rates of TRD across studies.

There are several different extant definitions of TRD. As a result, there are no agreed upon estimates of incidence or prevalence of the disorder.

Incidence:

In a Danish study of MDD patients, 14.0% developed TRD within 1 year of initial diagnosis, with an incidence rate of 163.6/1,000 PY (95% CI: 161.8-165.6) (Gronemann 2018). In this study, TRD was defined as 2 changes in treatment. In a study in Japan in which TRD was defined as 2 treatment failures in patients with an incident MDD diagnosis, 12.0% developed TRD within 1 year of the MDD diagnosis (Mahlich 2018).

A US study using administrative healthcare claims found that 10.4% of patients newly diagnosed with depression developed TRD within 1 year (Cepeda 2018). TRD was defined as having received either 3 distinct ADs or at least 1 antipsychotic in addition to an AD within 1 year.

Prevalence:

A review of the literature indicated that 30% to 50% of patients do not respond to an initial trial of AD medication (Trevino 2014). The CoBalT study, conducted in the UK, defined patients with TRD as those who scored ≥14 on the BDI II (ie, at least mild depression) after taking ADs for at least 6 weeks at an adequate dose (Thomas 2013). Of the patients studied, 55% met the definition for TRD. Results from the US STAR*D trial suggest that 35% of patients fail to respond to 2 trials of AD medication (Nemeroff 2007).

The European GSRD reported that 50.7% of a sample of 702 MDD patients were treatment-resistant, which was defined as not reaching a 17-item Hamilton Rating Scale for Depression score ≤17 (ie, at most mild depression), after at least 2 adequate consecutive AD trials administered during the last episode (Schosser 2012). Several scales have been used to assess TRD and response to therapy, including the MADRS (Johnson 2016).

Demographics of the Population in the Authorized Indication - Age, Sex, Ethnic Origin, and Risk Factors for the Disease

Age, Sex, and Ethnic Origin

In the European GSRD study, there were no demographic differences between patients with MDD only and patients with TRD. The mean age at onset of TRD was 36.8 years of age (standard deviation: 15.6) (Souery 2007). Most patients (75.3%) were female, and 58.7% of patients were married. The increased prevalence of TRD among women was also seen in the CoBalT study, in which 70.3% of patients were female (Thomas 2013). A literature review showed that patients with TRD were predominantly non-Hispanic white (89%) and female (71%), with an average age of 46.7 years (Mrazek 2014).

Risk Factors for the Disease

Risk factors for TRD include early age at onset of MDD and psychiatric and medical comorbidities, including anxiety, substance use disorders, insomnia, and pain (Cepeda 2018; Rizvi 2014). Other factors that have been associated with TRD include inflammatory system activation, abnormal neural activity, neurotransmitter dysfunction, melancholic clinical features, a higher traumatic load, more frequent and recurrent episodes of depression, and a longer duration of illness (Murphy 2017).

Main Existing Treatment Options:

Besides SPRAVATO, no other pharmacological treatments for patients with TRD are approved in the EU. Traditional treatments for MDD include psychotherapy and pharmacotherapy, with the main types of AD medication being SSRIs, SNRIs, atypical ADs, tricyclic ADs, and monoamine oxidase inhibitors (Mayo Clinic 2018). Pharmacotherapy is considered the first-line treatment for a major depressive episode (Bauer 2017). All approved AD pharmacotherapies work slowly over several weeks by acting on the same monoaminergic pathway. The World Federation of Societies of Biological Psychiatry recommends a careful review of the diagnosis and adequacy of dosing when patients do not respond to an AD treatment (Bauer 2017). Recommended strategies include: pharmacologic interventions with increasing dosage of an AD; switching to another AD within the same class; switching to a second AD in a different class; combining 2 ADs from different classes; or augmenting the AD. Augmentation strategies may involve the addition of lithium or an atypical antipsychotic (eg, quetiapine) to the AD. The AD may also be combined with psychotherapeutic intervention or other non-drug therapies such as electroconvulsive therapy.

Recently, novel non-pharmacologic and pharmacologic TRD treatments have emerged, including repetitive transcranial magnetic stimulation, intravenous/intranasal ketamine, VNS, deep brain stimulation, and buprenorphine (off-label use) (Conway 2017).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The STAR*D study was conducted among outpatients with nonpsychotic MDD who were candidates for medication as a first step in a series of 4 acute treatment steps (Rush 2006). Those who did not achieve remission or could not tolerate a treatment step were encouraged to move to the next step. Among those who entered the second step (after 1 failed trial), 55% relapsed within an average of 3.9 months. The overall relapse rate was higher with 2 and 3 failed trials (64.6% within an average of 3.1 subsequent months and 71.1% within an average of 3.3 subsequent months, respectively). Among those not in remission at entry to each step, the relapse rate was higher still, at 67.7%, 76%, and 83.3% within about 3 months.

In the STAR*D study, patients with TRD had more pronounced decreases in daily functioning and health-related quality of life scores, compared to non-TRD MDD patients (DiBernardo 2017).

Compared with other patients with MDD, those with TRD have lower productivity, higher medical comorbidity, and more suicide attempts. A lack of response to 2 adequate dose-duration trials of different established pharmacotherapy or psychotherapy classes is associated with a poor prognosis with respect to relapse and future treatment tolerance (Conway 2017). A systematic review of studies on follow-up treatment for patients with TRD, defined as failure to respond to at least 1 AD medication, reported that relapse rates rise with each successive step of treatment, from 55.3% at step 2 to 71.1% after step 4 (Fekadu 2009). Patients with TRD experience a more severe and protracted course of illness and are more likely to experience comorbid physical conditions than patients with MDD who do not develop treatment resistance. These patients are also more likely to have comorbid mental health problems, have significant short and long-term social impairment, and are more likely to attempt suicide (Vergunst 2013). Suicide attempt rates are 7-fold higher among TRD patients than MDD patients who are treatment responsive (Feldman 2013), and suicide-specific mortality rates were found to be 3.6 times higher in TRD patients compared with MDD patients without TRD or prior history of suicidality (Kern 2023). In summary, patients with TRD have a lower likelihood to respond to available oral ADs; these patients are more likely to have pronounced functional impairment, substantially lower quality of life, and incur higher medical and mental healthcare costs compared with patients who respond to treatment (Mathew 2012; Mrazek 2014).

There is evidence that TRD has a negative impact on mortality. Bergfeld and colleagues conducted a meta-analysis that included 30 studies to evaluate the suicide rate among TRD patients undergoing various types of treatment (Bergfeld 2018). The overall incidence of completed and attempted suicides was 0.47 and 4.66 per 100 PY, respectively. A Swedish study, which defined TRD patients as those having failed at least 3 treatment regimens, reported a 5-year relative survival of 0.97 compared to the general population and a 35% higher all-cause mortality compared to non-TRD MDD patients (adjusted hazard ratio 1.35; 95% CI: 1.21-1.50) (Reutfors 2018). Another Swedish register study found that patients with TRD experienced excess deaths in the range of 7 to 16 deaths per 1,000 patients during 5 years, with the highest excess risk in patients 18 to 29 years old (Brenner 2021).

An observational study of TRD patients in the US who had an inadequate response to at least 4 treatment regimens reported an all-cause mortality rate of 8.06 per 1,000 PY (95% CI: 0.00-16.99) for those who received TAU and 4.46 per 1,000 PY (95% CI: 0.00-9.41) for those who received VNS plus usual treatment (VNS + TAU) (Olin 2012). The suicide rate was 1.61 per 1,000 PY in the TAU group and 0.88 per 1,000 PY in the VNS + TAU group. Another US study, conducted in a Medicare population, compared TRD patients with managed depressed patients and reported a mortality rate of 46.2 per 1,000 PY in the first 2 years after the diagnosis was established for the TRD sample, and 46.8 per 1,000 PY for the same period for the managed depression population (Feldman 2013).

In a Danish study, depression was associated with excess mortality for both natural and unnatural causes (Laursen 2016). The authors reported an overall mortality rate ratio of 2.07 (95% CI: 2.05-2.09) for unipolar depression, 4.66 (95% CI: 4.53-4.79) for unnatural causes, and 1.98 (95% CI: 1.97-2.00) for natural causes.

Important Comorbidities:

The following are major comorbidities associated with TRD:

- Hypertension (Mrazek 2014);
- Joint, limb, or back pain (Mrazek 2014);
- Dyslipidemia (Mrazek 2014);
- Other psychiatric conditions, such as anxiety or personality disorder (Mrazek 2014);
- Suicidal ideation (Mrazek 2014);
- Obesity (Rizvi 2014);
- Headache/migraine (Kubitz 2013);
- Sleep disorder (Kubitz 2013).

Acute short-term treatment of psychiatric emergency due to MDD

Suicidal ideation is a common symptom in psychiatric emergency, as MDD is the psychiatric condition most commonly associated with suicide (Kessler 2005; Hawton 2013). Therefore, suicide-related morbidity and mortality in patients with MDD are a major public health concern (Kessler 2005; Wasserman 2012).

Incidence:

The incidence of MDD requiring an ED visit has not been identified for the EU.

According to the National Center for Health Statistics, in 2015 there were 304,272 ED visits with a primary diagnosis of unspecified MDD. Additionally, there were 38,383 visits with moderate and 39,931 visits with severe MDD (National Center for Health Statistics [b]).

The same study counted 8,166,861 physician office visits for unspecified MDD that year. Additionally, there were 1,311,677 moderate and 1,991,170 severe MDD physician office visits (National Center for Health Statistics [a]).

Prevalence:

An analysis of the NESARC-III conducted in 2012 to 2013 showed that nearly half (49.5%) of lifetime MDD patients had severe MDD. The finding was similar for those with onset in the prior 12-month period (46.8%) (Hasin 2018).

A study conducted in Germany a few years earlier (2009 to 2012) reported a lower incidence of severe MDD of 29.9% in men and 39.0% in women (Bretschneider 2018).

The World Health Organization World Mental Health Survey Initiative, in a general population-based sample, reported 12-month prevalence estimates of suicidal ideation, plans and attempts of 2.0%, 0.6%, and 0.3%, respectively, for developed countries and 2.1%, 0.7%, and 0.4%, respectively for developing countries (Borges 2010). Lifetime estimates for prevalence of suicidal ideation, plans, and attempts were 9.2%, 3.1%, and 2.7%, respectively (Nock 2008).

Demographics of the Population in the Authorized Indication - Age, Sex, Ethnic Origin, and Risk Factors for the Disease

Age, Sex, and Ethnic Origin

Women typically have a twofold increased risk of major depression compared with men. The median age of onset of MDD is in the middle 20s (Kessler 2013).

Risk Factors for the Disease

Comorbid anxiety disorder and childhood adversities are risk factors for more severe depression (Markkula 2016). Lack of social support contributes to disease risk. People who are separated or divorced have significantly higher rates of major depression than those who are married (Kessler 2013). Risk factors for recurrent depression include symptoms of anxiety, recent adverse life events and a history of alcohol dependence in men (van Loo 2018). People with major depression are at greater risk of suicide compared to people without depression, and the risk of death by suicide may, in part, be related to the severity of the depression (US Department of Health & Human Services 2014).

Main Existing Treatment Options:

Patients with psychiatric emergency due to MDD are an acutely ill population that requires immediate intervention (Wasserman 2012). Besides SPRAVATO, there are no approved pharmacological treatments for the rapid reduction of the symptoms of depression in this patient population (van der Feltz-Cornelis 2011; Zalsman 2016; Ionescu 2021). Furthermore, only limited information is available to guide clinical decisions, since this population has typically been excluded from AD drug trials in the past. Current standard practice includes initiation or optimization of oral ADs and, frequently, hospitalization (American Psychiatric Association 2003;

Wasserman 2012). Standard ADs may take several weeks to exert their full effect (Machado-Vieira 2010) limiting their utility in crisis situations.

ADs are the treatment of choice for the relief of depressive symptoms and suicidal ideation, which often accompanies depression, with SSRIs considered first-line therapy in primary care settings (Schwartz-Lifshitz 2012). Electroconvulsive therapy has also been used as treatment for acute suicidality among severely depressed patients (Schwartz-Lifshitz 2012).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Depression severity is inversely associated with remission and recovery as measured by the BDI (Markkula 2016). Exogenous factors can contribute to elevated risk of suicide attempt, including stressful life events and interpersonal and financial difficulties. Perceptions of these stressful life situations can be strongly distorted by psychiatric disorders. In the context of MDD, existing private, professional, or health issues may be magnified (Hegerl 2016). Physical illness and disability can, in some patients, contribute to the risk of suicidal thoughts and behaviors.

A UK Study reported the age- and sex-SMRs for all-cause mortality in depression was 2.55 (95% CI 2.45-2.65) (Das-Munshi 2019).

A Norwegian study reported an SMR of 23.9 (95% CI 18.0-31.8) for suicide in patients with MDD from 1980 to 2012 compared to the general Norwegian population (Hoye 2016). In the US, the Department of Health & Human Services estimates that 2% of people ever treated for depression as an outpatient will die by suicide (US Department of Health & Human Services 2014).

Important Comorbidities:

Comorbid conditions associated with MDD include the following:

- Cardiovascular diseases (Hirschfeld 2002)
- Acquired immune deficiency syndrome (Hirschfeld 2002)
- Cancer (Hirschfeld 2002)
- Alcohol dependence (Hirschfeld 2002)
- Neurological conditions (Hirschfeld 2002)
- Type 2 diabetes (Mezuk 2008)
- Anxiety disorders (Markkula 2016).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
Repeat-dose toxicity studies of 3 and 6 months in rats and 3 and 9 months in dogs were conducted with esketamine hydrochloride administered intranasally. Once-daily intranasal administration of esketamine in rats up to 9 mg/day for 6 months and dogs up to 72 mg/day for 9 months resulted in CNS-related clinical signs considered non-adverse, reflecting the anesthetic properties of the test article. Higher dose levels could not be achieved in these studies due to limitations associated with the long-term intranasal instillation of esketamine in rats and dogs. In the 6 month repeat-dose toxicity study in rats, hyperplasia of the olfactory epithelium was found at 9 mg/day and in a single female at 3 mg/day. In the 9-month repeat-dose toxicity study in dogs, focal atrophy of the olfactory epithelium was observed in the nasal cavity of males at 48 and 72 mg/day. There was no damage to the epithelium of the nasal turbinates, such as ulceration, metaplasia, or dysplasia, nor any evidence of pre-neoplastic lesions. Consequently, the microscopic changes observed in the nasal cavity of rats and dogs reflected a non-adverse local response to the long-term administration of esketamine. After 3 months of daily administration at 9 mg/day, the systemic exposure of esketamine in rats (C_{max} and AUC) resembled that in humans at the MRHD of 84 mg; the C_{max}- and AUC-based exposure ratios for esketamine in dogs after 3 months of daily administration at 72 mg/day were approximately 4- and 1-fold, respectively.	The nonclinical data do not indicate a safety concern for humans.
Reproductive toxicity	
No adverse findings with intranasal esketamine were observed in fertility and embryonic developmental toxicity and pre- and postnatal developmental toxicity studies in rats. The latter study included assessment of the offspring following exposure to esketamine via the breast milk. Published data indicate that ketamine induces developmental neurotoxicity in animals. Ketamine administered intravenously at high anesthetic dose levels to female rats in the second trimester of	Although no adverse effects on fertility or development were observed following administration of intranasal esketamine in rats, the possibility of developmental neurotoxicity of esketamine in humans cannot be excluded based on published findings following administration of ketamine in animals. In the offspring of pregnant rabbits treated with intranasal ketamine, skeletal malformations were noted at maternally toxic dose levels.

Key Safety Findings	Relevance to Human Usage
pregnancy caused neuronal cell abnormalities in the brains of their offspring, which exhibited behavioral changes and impaired memory up to young adult age (Zhao 2014). When female monkeys were treated intravenously with ketamine at high anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses (Brambrink 2012; Slikker 2007). Ketamine-induced neuronal cell death was also observed following early postnatal intraperitoneal or subcutaneous administration of ketamine to rat and mice pups during a period of rapid brain growth (Fredriksson 2004; Scallet 2004; Young 2005; Zou 2009). This period of brain development is equivalent to the third trimester of human pregnancy (Semple 2013). In an embryo-fetal developmental toxicity study in pregnant rats, intranasally administered ketamine did not induce adverse findings in the offspring. In an embryo-fetal developmental toxicity study with intranasally administered ketamine in pregnant rabbits, the offspring showed skeletal malformations at maternally toxic dose levels.	A relationship to ketamine treatment cannot be excluded. The use of SPRAVATO is not recommended during pregnancy.
Genotoxicity	
A series of in vitro and in vivo genotoxicity studies have been conducted with esketamine. The findings from these studies indicate that esketamine poses no genotoxic risk to humans.	Nonclinical data do not indicate a safety concern for humans.
Carcinogenicity	
No evidence of carcinogenic potential was observed following intranasal administration of esketamine in rats and subcutaneous administration of esketamine in transgenic mice.	Nonclinical data do not indicate a safety concern for humans.
Safety pharmacology	
Cardiovascular system (including potential for QT interval prolongation)	
Transient increases in blood pressure and heart rate occurred following intravenous administration of esketamine in dogs at exposures resembling those in humans at 84 mg.	Transient increases in blood pressure, as well as cardiovascular effects due to increased blood pressure, are expected in humans using SPRAVATO. Blood pressure increased is an important identified risk for SPRAVATO.

Key Safety Findings	Relevance to Human Usage
Nervous system	
In single-dose and 14-day repeated-dose neurotoxicity studies with intranasally-administered esketamine in rats, no evidence of histopathological brain lesions was noted. In single-dose neurotoxicity studies in which rats were intranasally administered esketamine at a dose up to 72 mg, the C_{max}- and AUC-based safety margins for esketamine were approximately 59- and 86-fold, respectively, the human exposure at the MRHD of 84 mg. In a 14-day neurotoxicity study in which rats were intranasally administered esketamine once daily up to a dose of 54 mg/day, the C_{max}- and AUC-based safety margins for esketamine were approximately 17- and 11-fold, respectively, the human exposure at the MRHD of 84 mg. Moreover, no evidence of neurotoxicity was found in the 6-month rat and the 9-month dog repeated-dose toxicology studies with once daily intranasal administration of esketamine as judged by brain histopathology (rats and dogs), neurobehavioral observations (rats) and neurological examinations (dogs). Similarly, no neurotoxicity was noted in shorter-term animal toxicology studies in which esketamine was intranasally administered.	The nonclinical data do not indicate a safety concern for humans.
Nephrotoxicity	
No evidence of nephrotoxicity was observed following intranasal administration of esketamine in rats and dogs for up to 6 and 9 months, respectively.	Nonclinical data do not indicate a safety concern for humans.
Hepatotoxicity	
No evidence of hepatotoxicity was observed following intranasal administration of esketamine in rats and dogs for up to 6 and 9 months, respectively.	Nonclinical data do not indicate a safety concern for humans.
Urinary bladder toxicity	
No evidence of urinary bladder toxicity was observed following intranasal administration of esketamine in rats and dogs for up to 6 and 9 months, respectively.	Nonclinical data do not indicate a safety concern for humans.
Juvenile neurotoxicity	
No evidence of neurotoxicity was observed in juvenile rats following subcutaneous administration of esketamine for up to 14 days or intranasal administration for up to 5.5 weeks.	Nonclinical data do not indicate a safety concern for humans.

Key Safety Findings	Relevance to Human Usage
Abuse potential	
Published data indicate that ketamine has abuse potential in animals.	SPRAVATO is expected to have abuse potential in humans. Drug abuse is an important identified risk for SPRAVATO.

Summary of Nonclinical Safety Concerns

Important identified risks	Drug abuse Blood pressure increased
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

Janssen Research & Development has developed esketamine nasal spray for 2 indications: TRD and acute short-term treatment of psychiatric emergency due to MDD. Compared to ketamine, esketamine has a higher NMDAR affinity that allows a lower volume of medication to be administered via the non-invasive and rapidly-absorbed intranasal route.

Data from the following TRD clinical trials are included in this RMP:

- Trial ESKETINTRD2003: A Phase 2a, randomized, double-blind, placebo-controlled adjunctive trial of intranasal esketamine in an adaptive treatment protocol to assess safety and efficacy in TRD;
- Trial ESKETINTRD3001: A Phase 3, randomized, double-blind, active-controlled trial to evaluate fixed doses of intranasal esketamine plus an oral AD in adult patients with TRD;
- Trial ESKETINTRD3002: A Phase 3, randomized, double-blind, active-controlled trial to evaluate flexible doses of intranasal esketamine plus an oral AD in adult patients with TRD;
- Trial ESKETINTRD3003: A Phase 3, double-blind, randomized withdrawal trial to assess the relative safety and efficacy of continuation versus discontinuation of esketamine nasal spray, in the presence of an ongoing oral AD, in adult patients with TRD who were in stable remission;
- Trial ESKETINTRD3004: A Phase 3, open-label, long-term trial of intranasal esketamine in adult patients with TRD;
- Trial ESKETINTRD3005: A Phase 3, randomized, double-blind, active-controlled trial to evaluate efficacy, safety, and tolerability of intranasal esketamine plus an oral AD in elderly patients with TRD.
- Trial 54135419TRD3008: An open-label long-term extension safety study of intranasal esketamine in TRD.

Data from the following MDSI clinical trials in adults are included in this RMP:

- Trial ESKETINSUI2001: A double-blind, randomized, placebo controlled study to evaluate the efficacy and safety of intranasal esketamine for the rapid reduction of the symptoms of MDD, including suicidal ideation, in subjects assessed to be at imminent risk for suicide;
- Trial 54135419SUI3001 (ASPIRE I): A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive SOC for the rapid reduction of the symptoms of MDD, including suicidal ideation, in adult subjects assessed to be at imminent risk for suicide;
- Trial 54135419SUI3002 (ASPIRE II): A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive SOC for the rapid reduction of the symptoms of MDD, including suicidal ideation, in adult subjects assessed to be at imminent risk for suicide.

SIII.2. Clinical Trial Exposure

The TRD clinical trials population includes 7 clinical trials:

- 5 randomized, blinded clinical trials:
  - ESKETINTRD2003 (TRD2003);
  - ESKETINTRD3001 (TRD3001);
  - ESKETINTRD3002 (TRD3002);
  - ESKETINTRD3003 (TRD3003);
  - ESKETINTRD3005 (TRD3005).
- 2 open-label clinical trials:
  - ESKETINTRD3004 (TRD3004).
  - 54135419TRD3008 (TRD3008).

The MDSI population includes 3 clinical trials (all randomized, blinded clinical trials):

- ESKETINSUI2001;
- 54135419SUI3001;
- 54135419SUI3002.

Exposure in Randomized, Blinded Clinical Trials

The following clinical trials were included in the TRD All Randomized, Blinded Trials Population (N=571): TRD3001 (double-blind phase), TRD3002 (double-blind phase), TRD3003 (double-blind maintenance phase), TRD3005 (double-blind phase), and TRD2003 (double-blind phase, excluding esketamine 14 mg, as this is not a recommended treatment dose). For the MDSI All Randomized, Blinded Trials Population (N=262), the following clinical trials were included: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

Exposure to esketamine nasal spray in the TRD and MDSI **All Randomized, Blinded Trials** Populations is summarized in Tables SIII.1 through SIII.5 for all patients by duration, by age group and sex, by dose, by race, and by special populations (renal function at baseline, hepatic function at baseline).

Table SIII.1: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Duration (Safety Analysis Set)

Cumulative for all indications		
Duration of exposure	**Patients**	**Patient-years**
≤28 days	677	38.6
29 to ≤56 days	25	2.6
57 to ≤84 days	33	6.2
85 to ≤112 days	11	2.9
>112 days	87[a]	57.5
Total	833	107.9
INDICATION: Treatment-resistant major depressive disorder		
Duration of exposure	**Patients**	**Patient-years**
≤28 days	419	23.2
29 to ≤56 days	21	2.3
57 to ≤84 days	33	6.2
85 to ≤112 days	11	2.9
>112 days	87[a]	57.5
Total	571	92.1
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
Duration of exposure	**Patients**	**Patient-years**
≤28 days	258	15.5
29 to ≤56 days	4	0.3
57 to ≤84 days	0	-
85 to ≤112 days	0	-
>112 days	0	-
Total	262	15.8

Trials included in the TRD All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg).

Trials included in the MDSI All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

The duration of exposure includes days between dosing sessions on which subjects did not actually take trial medication.

[a:] Includes 54 subjects with ≥6 months (180 days) exposure and 14 subjects with ≥12 months (350 days) exposure.

Source: adapted from the following outputs:

- All indications: [TSIEXP01C.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP01C.SAS] 13NOV2019, 16:24
- TRD: [TSIEXP01A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2018\RE_RMP2018\PROD\TSIEXP01A.SAS] 03AUG2018, 15:55
- MDSI: [TSIEXP01A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP01A.SAS] 17MAY2019, 15:41

Table SIII.2: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Age Group and Sex (Safety Analysis Set)

Cumulative for all indications				
	Men		**Women**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**
18 to 25 years	35	2.0	45	5.9
26 to 50 years	140	17.4	272	39.4
51 to 64 years	104	14.7	165	23.9
65 to 74 years	22	1.4	37	2.5
75 to 84 years	5	0.3	7	0.4
≥85 years	0	0	1	0.1
Total	306	35.7	527	72.2
INDICATION: Treatment-resistant major depressive disorder				
	Men		**Women**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**
18 to 25 years	10	0.7	16	4.1
26 to 50 years	93	14.4	184	34.3
51 to 64 years	71	12.8	125	21.3
65 to 74 years	22	1.4	37	2.5
75 to 84 years	5	0.3	7	0.4
≥85 years	0	0	1	0.1
Total	201	29.5	370	62.7
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior				
	Men		**Women**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**
18 to 25 years	25	1.3	29	1.8
26 to 50 years	47	3.0	88	5.1
51 to 64 years	33	1.9	40	2.6
65 to 74 years	0	-	0	-
75 to 84 years	0	-	0	-
≥85 years	0	-	0	-
Total	105	6.2	157	9.5

Trials included in the TRD All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg).
Trials included in the MDSI All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).
The duration of exposure includes days between dosing sessions on which subjects did not actually take trial medication.
Source: adapted from the following outputs:

- All indications: [TSIEXP02C.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP02C.SAS] 13NOV2019, 16:24
- TRD: [TSIEXP02A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2018\RE_RMP2018\PROD\TSIEXP02A.SAS] 03AUG2018, 15:55
- MDSI: [TSIEXP02A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP02A.SAS] 17MAY2019, 15:41

Table SIII.3: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Dose (Safety Analysis Set)

Cumulative for all indications		
Dose of exposure	**Patients**	**Patient-years**
28 mg	19	0.4
56 mg	147	17.5
84 mg	395	30.1
Flexible dose	272	60.0
Total	833	107.9
INDICATION: Treatment-resistant major depressive disorder		
Dose of exposure	**Patients**	**Patient-years**
28 mg	19	0.4
56 mg	147	17.5
84 mg	133	14.3
Flexible dose	272	60.0
Total	571	92.1
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
Dose of exposure	**Patients**	**Patient-years**
84 mg	262	15.8
Total	262	15.8

Trials included in the TRD All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg).
Trials included in the MDSI All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).
The duration of exposure includes days between dosing sessions on which subjects did not actually take trial medication.
Source: adapted from the following outputs:

- All indications: [TSIEXP03C.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP03C.SAS] 13NOV2019, 16:24
- TRD: [TSIEXP03A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2018\RE_RMP2018\PROD\TSIEXP03A.SAS] 03AUG2018, 15:55
- MDSI: [TSIEXP03A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP03A.SAS] 13NOV2019, 16:24

Table SIII.4: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Race (Safety Analysis Set)

Cumulative for all indications		
Race	**Patients**	**Patient-years**
White	659	91.3
Black or African American	64	7.0
Asian	46	2.3
Other[a]	64	7.2
Total	833	107.9
INDICATION: Treatment-resistant major depressive disorder		
Race	**Patients**	**Patient-years**
White	470	79.9
Black or African American	40	5.6
Asian	16	0.6
Other[a]	45	6.1
Total	571	92.1
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
Race	**Patients**	**Patient-years**
White	189	11.4
Black or African American	24	1.4
Asian	30	1.8
Other[a]	19	1.2
Total	262	15.8

Trials included in the TRD All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg).

Trials included in the MDSI All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

The duration of exposure includes days between dosing sessions on which subjects did not actually take trial medication.

[a:] 'Other' includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Not Reported, Other, and Unknown.

Source: adapted from the following outputs:

- All indications: [TSIEXP04C.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP04C.SAS] 13NOV2019, 16:25
- TRD: [TSIEXP04A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2018\RE_RMP2018\PROD\TSIEXP04A.SAS] 03AUG2018, 15:55
- MDSI: [TSIEXP04A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP04A.SAS] 17MAY2019, 15:41

Table SIII.5: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Special Populations (Safety Analysis Set)

Cumulative for all indications		
	Patients	**Patient-years**
Renal function at baseline[a]		
Normal (CrCl ≥90 mL/min)	243	42.7
Mild (CrCl 60 to <90 mL/min)	94	12.2
Moderate (CrCl 30 to <60 mL/min)	20	1.6
Severe (CrCl <30 mL/min)	0	-
Missing	214	35.6
Total	571	92.1
Hepatic function at baseline		
ALT		
≤ULN (normal)	729	93.1
>ULN to ≤3.0×ULN	93	14.2
>3.0×ULN to ≤5.0×ULN	3	0.2
>5.0×ULN	0	-
Missing	8	0.5
Total	833	107.9
AST		
≤ULN (normal)	777	103.1
>ULN to ≤3.0×ULN	42	3.9
>3.0×ULN to ≤5.0×ULN	0	-
>5.0×ULN	0	-
Missing	14	1.0
Total	833	107.9
Bilirubin		
≤ULN (normal)	813	106.2
>ULN to ≤1.5×ULN	12	1.3
>1.5×ULN to ≤3.0×ULN	2	0.1
>3.0×ULN	0	-
Missing	6	0.4
Total	833	107.9
Hepatic function at baseline[b]		
Normal	716	91.7
Mild	107	15.6
Moderate	2	0.1
Severe	0	-
Missing	8	0.5
Total	833	107.9
INDICATION: Treatment-resistant major depressive disorder		
	Patients	**Patient-years**
Renal function at baseline[c]		
Normal (CrCl ≥90 mL/min)	243	42.7
Mild (CrCl 60 to <90 mL/min)	94	12.2
Moderate (CrCl 30 to <60 mL/min)	20	1.6
Severe (CrCl <30 mL/min)	0	-
Missing	214	35.6
Total	571	92.1
Hepatic function at baseline[d]		
ALT		
≤ULN (normal)	500	79.2
>ULN to ≤3.0×ULN	68	12.8
>3.0×ULN to ≤5.0×ULN	3	0.2
>5.0×ULN	0	-
Missing	0	-
Total	571	92.1

Table SIII.5: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Special Populations (Safety Analysis Set)

Hepatic function at baseline[d]		
AST		
≤ULN (normal)	538	88.6
>ULN to ≤3.0×ULN	31	3.3
>3.0×ULN to ≤5.0×ULN	0	-
>5.0×ULN	0	-
Missing	2	0.2
Total	571	92.1
Bilirubin		
≤ULN (normal)	564	91.2
>ULN to ≤1.5×ULN	5	0.9
>1.5×ULN to ≤3.0×ULN	2	0.1
>3.0×ULN	0	-
Missing	0	-
Total	571	92.1
Hepatic function at baseline[b]		
Normal	493	78.3
Mild	76	13.8
Moderate	2	0.1
Severe	0	-
Missing	0	-
Total	571	92.1
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
	Patients	**Patient-years**
Renal function at baseline[a]		
N/A		
Hepatic function at baseline		
ALT		
≤ULN (normal)	229	13.9
>ULN to ≤3.0×ULN	25	1.4
>3.0×ULN to ≤5.0×ULN	0	-
>5.0×ULN	0	-
Missing	8	0.5
Total	262	15.8
AST		
≤ULN (normal)	239	14.4
>ULN to ≤3.0×ULN	11	0.6
>3.0×ULN to ≤5.0×ULN	0	-
>5.0×ULN	0	-
Missing	12	0.8
Total	262	15.8
Bilirubin		
≤ULN (normal)	249	15.0
>ULN to ≤1.5×ULN	7	0.4
>1.5×ULN to ≤3.0×ULN	0	-
>3.0×ULN	0	-
Missing	6	0.4
Total	262	15.8

Table SIII.5: Clinical Trial Exposure for Esketamine in Randomized, Blinded Trials by Special Populations (Safety Analysis Set)

Hepatic function at baseline		
Hepatic function at baseline[b]		
Normal	223	13.5
Mild	31	1.8
Moderate	0	-
Severe	0	-
Missing	8	0.5
Total	262	15.8

Trials included in the TRD All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg).
Trials included in the MDSI All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).
The duration of exposure includes days between dosing sessions on which subjects did not actually take trial medication.

a: Creatinine clearance was not collected for trials ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 so renal function cannot be determined and is not included for these trials.

b: Normal: Total bilirubin ≤ ULN and ALT ≤ ULN;
Mild: (Total bilirubin ≤ ULN and ALT > ULN) or (ULN < Total bilirubin ≤1.5×ULN);
Moderate: 1.5×ULN < Total bilirubin ≤3×ULN;
Severe: Total bilirubin >3×ULN.

c: Subjects with severe renal impairment (CrCl <30 mL/min) were excluded from the Phase 3 clinical trials.

d: Subjects with liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time), ALT or AST ≥2×ULN, or total bilirubin >1.5×ULN (unless elevation was consistent with Gilbert's disease) were excluded from the Phase 3 trials.

Source: adapted from the following outputs:

- All indications:
[TSIEXP05C.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP05C.SAS] 13NOV2019, 16:25
- TRD: [TSIEXP05A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2018\RE_RMP2018\PROD\TSIEXP05A.SAS] 03AUG2018, 15:55
- MDSI: [TSIEXP05A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP05A.SAS] 17MAY2019, 15:41

Exposure in All Clinical Trials

The following clinical trials were included in the TRD All Clinical Trials Population (N=1,889): TRD3001, TRD3002, TRD3003, TRD3004, TRD3005, TRD3008, and TRD2003. The following clinical trials were included in the MDSI All Clinical Trials Population (N=262): ESKETINSUI2001, 54135419SUI3001, and 54135419SUI3002.

Exposure to esketamine nasal spray in the **All Clinical Trials** Population is summarized in Tables SIII.6 through SIII.10 for all patients by duration, by age group and sex, by dose, by race, and by special populations (renal function at baseline, hepatic function at baseline).

Table SIII.6: Clinical Trial Exposure for Esketamine in All Clinical Trials by Duration (Safety Analysis Set)

Cumulative for all indications		
Duration of exposure	**Patients**	**Patient-years**
≤1 Month (Day ≤28)	730	36.3
1 to ≤3 months	167	25.3
3 to ≤6 months	107	34.4
6 to ≤12 months	128	85.0
12 to ≤24 months	133	172.1
24 to ≤36 months	89	200.1
36 to ≤48 months	159	528.2
48 to ≤60 months	145	592.7
60 to ≤72 months	228	1166.4
72 to ≤84 months	256	1504.4
>84 months	9	59.3
Total	2151	4404.1
INDICATION: Treatment-resistant major depressive disorder		
Duration of exposure	**Patients**	**Patient-years**
≤1 Month (Day ≤28)	472	20.8
1 to ≤3 months	163	25.0
3 to ≤6 months	107	34.4
6 to ≤12 months	128	85.0
12 to ≤24 months	133	172.1
24 to ≤36 months	89	200.1
36 to ≤48 months	159	528.2
48 to ≤60 months	145	592.7
60 to ≤72 months	228	1166.4
72 to ≤84 months	256	1504.4
>84 months	9	59.3
Total	1889	4388.3
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
Duration of exposure	**Patients**	**Patient-years**
≤28 days	258	15.5
29 to ≤56 days	4	0.3
57 to ≤84 days	0	-
85 to ≤112 days	0	-
>112 days	0	-
Total	262	15.8

Trials included in the TRD All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg). Note: Population (N=1889) includes 1 subject dosed with oral antidepressant only during ESKETINTRD3004 after completing ESKETINTRD3005 on placebo. The exposure to esketamine was 0 in that subject.

Trials included in the MDSI All Clinical Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

The duration of exposure includes days between dosing sessions on which subjects did not actually take study medication.

Source: adapted from the following outputs:

- All indications: [tsiexp01d.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_pool/tsiexp01d.sas] 18JUL2023, 08:08
- TRD: [tsiexp01b.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsiexp01b.sas] 06JUL2023, 06:20
- MDSI: [TSIEXP01A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP01A.SAS] 17MAY2019, 15:41

Table SIII.7: Clinical Trial Exposure for Esketamine in All Clinical Trials by Age Group and Sex (Safety Analysis Set)

Cumulative for all indications				
	Men		**Women**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**
18 to 25 years	63	58.7	68	76.7
26 to 50 years	384	674.7	658	1516.5
51 to 64 years	284	551.5	497	1127.8
65 to 74 years	62	114.3	109	245.4
75 to 84 years	8	13.5	16	24.4
≥85 years	0	0	2	0.6
Total	801	1412.7	1350	2991.4
INDICATION: Treatment-resistant major depressive disorder				
	Men		**Women**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**
18 to 25 years	38	57.4	39	74.9
26 to 50 years	337	671.7	570	1511.4
51 to 64 years	251	549.6	457	1125.2
65 to 74 years	62	114.3	109	245.4
75 to 84 years	8	13.5	16	24.4
≥85 years	0	0	2	0.6
Total	696	1406.4	1193	2981.9
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior				
	Men		**Women**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**
18 to 25 years	25	1.3	29	1.8
26 to 50 years	47	3.0	88	5.1
51 to 64 years	33	1.9	40	2.6
65 to 74 years	0	-	0	-
75 to 84 years	0	-	0	-
≥85 years	0	-	0	-
Total	105	6.2	157	9.5

Trials included in the TRD All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg). Note: Population (N=1889) includes 1 subject dosed with oral antidepressant only during ESKETINTRD3004 after completing ESKETINTRD3005 on placebo. The exposure to esketamine was 0 in that subject.

Trials included in the MDSI All Clinical Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

The duration of exposure includes days between dosing sessions on which subjects did not actually take trial medication.

Source: adapted from the following outputs:

- All indications: [tsiexp02d.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_pool/tsiexp02d.sas] 18JUL2023, 08:08
- TRD: [tsiexp02b rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsiexp02b.sas] 07JUL2023, 03:30
- MDSI: [TSIEXP02A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP02A.SAS] 17MAY2019, 15:41

Table SIII.8: Clinical Trial Exposure for Esketamine in All Clinical Trials by Dose (Safety Analysis Set)

Cumulative for all indications		
Dose of exposure	**Patients**	**Patient-years**
28 mg	19	0.4
56 mg	147	30.1
84 mg	395	40.2
Flexible dose	1813	4333.0
Total	2151	4403.6
INDICATION: Treatment-resistant major depressive disorder		
Dose of exposure	**Patients**	**Patient-years**
28 mg	19	0.4
56 mg	147	30.1
84 mg	133	24.4
Flexible dose	1813	4333.0
Total	1889	4387.8[a]
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
Dose of exposure	**Patients**	**Patient-years**
84 mg	262	15.8
Total	262	15.8

Trials included in the TRD All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg). Note: Population (N=1889) includes 1 subject dosed with oral antidepressant only during ESKETINTRD3004 after completing ESKETINTRD3005 on placebo. The exposure to esketamine was 0 in that subject.

Trials included in the MDSI All Clinical Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

The duration of exposure includes days between dosing sessions on which subjects did not actually take study medication.

[a:] For ESKETINTRD2003, because the double-blind exposure is summarized by dose and the open-label exposure is summarized as flexible dosing, the total person-year calculation does not include exposure between the last double-blind dose and the first open-label dose.

Source: adapted from the following outputs:

- All indications: [tsiexp03d.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_pool/tsiexp03d.sas] 18JUL2023, 08:08
- TRD: [tsiexp03b rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsiexp03b.sas] 06JUL2023, 05:22
- MDSI: [TSIEXP03A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_POOLED\PROD\TSIEXP03A.SAS] 13NOV2019, 16:24

Table SIII.9: Clinical Trial Exposure for Esketamine in All Clinical Trials by Race (Safety Analysis Set)

Cumulative for all indications		
Race	**Patients**	**Patient-years**
White	1786	3833.2
Black or African American	105	142.6
Asian	159	183.0
Other[a]	101	245.3
Total	2151	4404.1
INDICATION: Treatment-resistant major depressive disorder		
Race	**Patients**	**Patient-years**
White	1597	3821.8
Black or African American	81	141.2
Asian	129	181.2
Other[a]	82	244.1
Total	1889	4388.3

Table SIII.9: Clinical Trial Exposure for Esketamine in All Clinical Trials by Race (Safety Analysis Set)

INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
Race	**Patients**	**Patient-years**
White	189	11.4
Black or African American	24	1.4
Asian	30	1.8
Other[a]	19	1.2
Total	262	15.8

Trials included in the TRD All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg). Note: Population (N=1889) includes 1 subject dosed with oral antidepressant only during ESKETINTRD3004 after completing ESKETINTRD3005 on placebo. The exposure to esketamine was 0 in that subject.
Trials included in the MDSI All Clinical Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).
The duration of exposure includes days between dosing sessions on which subjects did not actually take study medication.

a: 'Other' includes American Indian Or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Not Reported, Other, and Unknown.

Source: adapted from the following outputs:

- All indications: [tsiexp04d rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_pool/tsiexp04d.sas] 18JUL2023, 08:08
- TRD: [tsiexp04b rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsiexp04b.sas] 06JUL2023, 05:22
- MDSI: [TSIEXP04A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP04A.SAS] 17MAY2019, 15:41

Table SIII.10: Clinical Trial Exposure for Esketamine in All Clinical Trials by Special Populations (Safety Analysis Set)

Cumulative for all indications		
	Patients	**Patient-years**
Renal impairment at baseline[a]		
Normal (CrCl ≥90 mL/min)	770	2095.7
Mild (CrCl 60 to <90 mL/min)	296	732.0
Moderate (CrCl 30 to <60 mL/min)	45	84.9
Severe (CrCl <30 mL/min)	0	-
Missing	778	1475.8
Total	1889	4388.3
Hepatic impairment at baseline		
ALT		
≤ULN (normal)	1901	3917.8
>ULN to ≤3.0×ULN	232	466.2
>3.0×ULN to ≤5.0×ULN	6	9.5
>5.0×ULN	3	5.2
Missing	9	5.5
Total	2151	4404.1
AST		
≤ULN (normal)	2024	4173.9
>ULN to ≤3.0×ULN	106	193.9
>3.0×ULN to ≤5.0×ULN	2	5.9
>5.0×ULN	1	4.9
Missing	18	25.5
Total	2151	4404.1

Table SIII.10: Clinical Trial Exposure for Esketamine in All Clinical Trials by Special Populations (Safety Analysis Set)

Cumulative for all indications		
	Patients	**Patient-years**
Bilirubin		
≤ULN (normal)	2119	4357.7
>ULN to ≤1.5×ULN	21	34.2
>1.5×ULN to ≤3.0×ULN	4	9.5
>3.0×ULN	0	-
Missing	7	2.7
Total	2151	4404.1
Hepatic impairment at baseline[b]		
Normal	1878	3875.6
Mild	259	511.2
Moderate	4	9.5
Severe	0	-
Missing	10	7.8
Total	2151	4404.1
INDICATION: Treatment-resistant major depressive disorder		
	Patients	**Patient-years**
Renal impairment at baseline[c]		
Normal (CrCl ≥90 mL/min)	770	2095.7
Mild (CrCl 60 to <90 mL/min)	296	732.0
Moderate (CrCl 30 to <60 mL/min)	45	84.9
Severe (CrCl <30 mL/min)	0	-
Missing	778	1475.8
Total	1889	4388.3
Hepatic impairment at baseline[d]		
ALT		
≤ULN (normal)	1672	3903.9
>ULN to ≤3.0×ULN	207	464.8
>3.0×ULN to ≤5.0×ULN	6	9.5
>5.0×ULN	3	5.2
Missing	1	5.0
Total	1889	4388.3
AST		
≤ULN (normal)	1785	4159.5
>ULN to ≤3.0×ULN	95	193.3
>3.0×ULN to ≤5.0×ULN	2	5.9
>5.0×ULN	1	4.9
Missing	6	24.8
Total	1889	4388.3
Bilirubin		
≤ULN (normal)	1870	4342.7
>ULN to ≤1.5×ULN	14	33.8
>1.5×ULN to ≤3.0×ULN	4	9.5
>3.0×ULN	0	-
Missing	1	2.4
Total	1889	4388.3
Hepatic impairment at baseline[b]		
Normal	1655	3862.1
Mild	228	509.4
Moderate	4	9.5
Severe	0	-
Missing	2	7.3
Total	1889	4388.3

Table SIII.10: Clinical Trial Exposure for Esketamine in All Clinical Trials by Special Populations (Safety Analysis Set)

Cumulative for all indications		
	Patients	**Patient-years**
INDICATION: Major depressive disorder in patients who have current suicidal ideation or behavior		
	Patients	**Patient-years**
Renal impairment at baseline[a]		
N/A		
Hepatic impairment at baseline		
ALT		
≤ULN (normal)	229	13.9
>ULN to ≤3.0×ULN	25	1.4
>3.0×ULN to ≤5.0×ULN	0	-
>5.0×ULN	0	-
Missing	8	0.5
Total	262	15.8
AST		
≤ULN (normal)	239	14.4
>ULN to ≤3.0×ULN	11	0.6
>3.0×ULN to ≤5.0×ULN	0	-
>5.0×ULN	0	-
Missing	12	0.8
Total	262	15.8
Bilirubin		
≤ULN (normal)	249	15.0
>ULN to ≤1.5×ULN	7	0.4
>1.5×ULN to ≤3.0×ULN	0	-
>3.0×ULN	0	-
Missing	6	0.4
Total	262	15.8
Hepatic impairment at baseline[b]		
Normal	223	13.5
Mild	31	1.8
Moderate	0	-
Severe	0	-
Missing	8	0.5
Total	262	15.8

Trials included in the TRD All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg). Note: Population (N=1889) includes 1 subject dosed with oral antidepressant only during ESKETINTRD3004 after completing ESKETINTRD3005 on placebo. The exposure to esketamine was 0 in that subject.
Trials included in the MDSI All Clinical Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).
The duration of exposure includes days between dosing sessions on which subjects did not actually take study medication.

a: Creatinine clearance was not collected for trials ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 so renal function cannot be determined and is not included for these trials.

b: Normal: Total bilirubin ≤ ULN and ALT ≤ ULN;
Mild: (Total bilirubin ≤ ULN and ALT > ULN) or (ULN < Total bilirubin ≤1.5×ULN);
Moderate: 1.5×ULN < Total bilirubin ≤3×ULN;
Severe: Total bilirubin >3×ULN.

c: Subjects with severe renal impairment (CrCl <30 mL/min) were excluded from the Phase 3 clinical trials.

d: Subjects with liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time), ALT or AST ≥2×ULN, or total bilirubin >1.5×ULN (unless elevation was consistent with Gilbert's disease) were excluded from the Phase 3 trials.

Source: adapted from the following outputs:

- All indications:
[tsiexp05d rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_pool/tsiexp05d.sas] 18JUL2023, 08:08
- TRD: [tsiexp05b rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsiexp05b.sas] 06JUL2023, 05:22
- MDSI: [TSIEXP05A.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSIEXP05A.SAS] 17MAY2019, 15:41

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Cardiovascular disease (cerebrovascular disease with a history of stroke or transient ischemic attack; aneurysmal vascular disease; coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure within 12 months before the start of the trial; hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation; NYHA Class III-IV heart failure)**
Reason for being an exclusion criterion	Cardiovascular effects due to increased blood pressure are expected for esketamine nasal spray based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the CNS that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure, as well as cardiovascular and blood pressure-related events, in association with esketamine nasal spray were reported in the Phase 1 and 2 clinical trials in healthy volunteers and patients with MDD. Patients with pre-existing cardiovascular conditions for whom a sudden acute increase in blood pressure might pose a safety risk were therefore excluded from esketamine clinical trials.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO is contraindicated in patients for whom an increase in blood pressure poses a serious risk (SmPC Section 4.3, Contraindications). This includes patients with known aneurysmal vascular disease (including the intracranial, thoracic, or abdominal aorta or peripheral arterial vessels) and patients with a known history of intracerebral hemorrhage. Patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing SPRAVATO; treatment should be initiated only if the benefit outweighs the risk (SmPC Section 4.4, Special warnings and precautions for use).

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 2	**Uncontrolled hypertension or history of hypertensive crisis**
Reason for being an exclusion criterion	Increased blood pressure is expected for esketamine nasal spray based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the CNS that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure in association with esketamine nasal spray were reported in the Phase 1 and 2 clinical trials. Patients with unstable or poorly controlled hypertension may be at an increased risk of adverse cardiovascular effects. These patients were therefore excluded from esketamine clinical trials as presence of uncontrolled hypertension or a prior history of hypertensive crisis was considered to pose a safety risk.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO is contraindicated in patients for whom an increase in blood pressure poses a serious risk (SmPC Section 4.3, Contraindications). Blood pressure increased is an important identified risk.
Criterion 3	**Clinically significant electrocardiogram abnormalities**
Reason for being an exclusion criterion	Cardiovascular effects due to increased blood pressure are expected for esketamine nasal spray based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the CNS that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure, as well as cardiovascular and blood pressure-related events, in association with esketamine nasal spray have been reported in the Phase 1 and 2 clinical trials.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO is contraindicated in patients for whom an increase in blood pressure poses a serious risk (SmPC Section 4.3, Contraindications) and should be used with caution in patients with known uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability (SmPC Section 4.4, Special warnings and precautions for use).
Criterion 4a	**Pregnancy**
Reason for being an exclusion criterion	For ethical reasons, pregnant women are normally excluded from clinical trials. The possibility of developmental neurotoxicity in human fetuses exposed to esketamine in utero cannot be excluded based on published findings following administration of ketamine in animals.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO is not recommended during pregnancy; treatment should be discontinued if a woman becomes pregnant (SmPC Section 4.6, Fertility, pregnancy and lactation).

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 4b	**Breast-feeding women**
Reason for being an exclusion criterion	For ethical reasons, breast-feeding women are normally excluded from clinical trials. Ketamine is excreted in human milk (Wolfson 2023); therefore, it is expected that its S-enantiomer esketamine is excreted in human milk.
Included as missing information?	No
Rationale (if not included as missing information)	A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from SPRAVATO therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (SmPC Section 4.6, Fertility, pregnancy and lactation).
Criterion 5	**Liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time); ALT or AST ≥2×ULN; total bilirubin >1.5×ULN (unless elevation was consistent with Gilbert's disease)**
Reason for being an exclusion criterion	Esketamine is metabolized in the liver and hepatic clearance is required for termination of clinical effects. Abnormal liver function tests associated with the use of intravenous esketamine have been reported, particularly with extended use or drug abuse. Patients with severe hepatic impairment (Child Pugh class C) were excluded from esketamine clinical trials to reduce potential confounding of the assessment of safety.
Included as missing information?	No
Rationale (if not included as missing information)	The safety profile of SPRAVATO is not expected to differ in patients with mild/moderate hepatic impairment. SPRAVATO has not been studied in patients with severe hepatic impairment (Child Pugh class C) (SmPC Section 4.2, Posology and method of administration and Section 5.2 Pharmacokinetic properties) and is not recommended in patients with severe hepatic impairment (SmPC Section 4.2, Posology and method of administration and Special warnings and precautions for use, Section 4.4).
Criterion 6	**Patients <18 years of age**
Reason for being an exclusion criterion	It is standard practice to develop a drug in the adult population before the pediatric population unless the target disease is exclusively pediatric.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO is not indicated for use in patients <18 years of age.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 7	**Psychotic disorder or MDD with psychotic features, bipolar or related disorders, obsessive compulsive disorder, intellectual disability, autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder**
Reason for being an exclusion criterion	In general, patients with multiple psychiatric comorbidities were excluded from the Phase 2 and Phase 3 clinical trials so as not to confound the assessment of efficacy. Patients with psychiatric diagnoses other than the indications studied (eg, psychotic disorder, MDD with psychotic features, bipolar or related disorders, obsessive compulsive disorder, and autism spectrum disorder) were excluded from the Phase 3 clinical trials as these would require separate investigation. In addition, patients with a diagnosis of MDD with psychoses represented a more vulnerable population in whom ketamine may cause psychotomimetic symptoms; therefore, these patients were excluded from esketamine clinical trials. Patients with the other psychiatric comorbidities (ie, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, and narcissistic personality disorder) were excluded so as not to confound the assessment of efficacy.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO should be used with caution in patients with a presence or history of psychosis, mania, or bipolar disorder; these patients should be carefully assessed before prescribing SPRAVATO, and treatment should be initiated only if the benefit outweighs the risk (SmPC Section 4.4, Special warnings and precautions for use). SPRAVATO may be used in patients with psychiatric comorbidities other than psychosis.
Criterion 8	**Homicidal ideation/intent**
Reason for being an exclusion criterion	Patients with active homicidal ideation or intent were not included for safety and ethical reasons (risk to the investigative staff).
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO may be used in patients who exhibit homicidal ideation or intent.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 9	**Evidence of moderate to severe substance use or alcohol use disorder**
Reason for being an exclusion criterion	Current or recent evidence of moderate or severe substance or alcohol use disorder could interfere with clinical improvement and interpretation of the efficacy and safety results. Evidence from a human abuse potential study (Trial 54135419TRD1015) suggests that the potential for abuse with esketamine is similar to that of ketamine; therefore, patients with evidence of moderate or severe substance or alcohol use disorder may be at increased risk for abuse.
Included as missing information?	No
Rationale (if not included as missing information)	An individual's risk for abuse or misuse should be assessed before SPRAVATO is prescribed, and patients receiving SPRAVATO should be monitored for the development of behaviors or conditions of abuse or misuse while on therapy (SmPC Section 4.4, Special warnings and precautions for use). Drug abuse is an important identified risk.
Criterion 10	**Thyroid disease/disorder**
Reason for being an exclusion criterion	Ketamine is associated with an increased risk of hypertension and tachycardia in patients with hyperthyroidism or patients receiving thyroid replacement. Hyperthyroidism increases the risk of cardiovascular symptoms with use of esketamine. In addition, untreated thyroid disease may be associated with the presence of depressive symptoms; such patients were therefore excluded so as not to confound the assessment of efficacy.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO should be used with caution in patients with hyperthyroidism that has not been sufficiently treated; these patients should be carefully assessed before prescribing SPRAVATO, and treatment should be initiated only if the benefit outweighs the risk (SmPC Section 4.4, Special warnings and precautions for use).

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 11	**Significant pulmonary insufficiency**
Reason for being an exclusion criterion	Respiratory depression has been reported following injections of ketamine and esketamine, particularly after a high dose and/or rapid intravenous injection. Patients with significant pulmonary insufficiency were excluded from Phase 3 clinical trials. Treatment for the primary condition leading to pulmonary insufficiency is necessary first, as that is more immediate and life threatening.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO should be used with caution in patients with significant pulmonary insufficiency; these patients should be carefully assessed before prescribing SPRAVATO, and treatment should be initiated only if the benefit outweighs the risk (SmPC Section 4.4, Special warnings and precautions for use).
Criterion 12	**Untreated glaucoma, current penetrating or perforating eye injury, brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure or increased intraocular pressure or planned eye surgery**
Reason for being an exclusion criterion	Increased blood pressure is expected for esketamine nasal spray based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the CNS that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure in association with esketamine nasal spray have been reported in Phase 1 and 2 clinical trials. Intraocular or intracranial pressure could theoretically increase after administration of esketamine nasal spray.
Included as missing information?	No
Rationale (if not included as missing information)	SPRAVATO should be used with caution in patients with a history of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure; treatment should be initiated only if the benefit outweighs the risk (SmPC Section 4.4, Special warnings and precautions for use). Increased intraocular pressure is not expected when SPRAVATO is used at therapeutic doses.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 13	**Seizures**
Reason for being an exclusion criterion	Seizures/epilepsy may be associated with depression. The primary treatment for patients with depressive symptoms and seizures/epilepsy is treatment for the seizures with approved medications. Therefore, enrollment of such patients in esketamine clinical trials was not considered prudent.
Included as missing information?	No
Rationale (if not included as missing information)	The exclusion criterion was implemented for the purpose of the clinical trials and not for a specific safety concern. Seizures/epilepsy is not a contraindication or precaution for use of SPRAVATO.
Criterion 14	**Uncontrolled diabetes mellitus or history of diabetic ketoacidosis, hyperglycemic coma, or severe hypoglycemia with loss of consciousness**
Reason for being an exclusion criterion	These patients were excluded from the Phase 3 clinical trials to reduce potential confounding of the assessment of safety and efficacy. The presence of uncontrolled diabetes could confound the assessment and stability of depressive symptoms. Patients with controlled diabetes were included in the clinical trials.
Included as missing information?	No
Rationale (if not included as missing information)	The exclusion criterion was implemented for the purpose of the clinical trials and not for a specific safety concern.
Criterion 15	**Use of benzodiazepines at a daily dose greater than the equivalent of 6 mg/day of lorazepam**
Reason for being an exclusion criterion	High doses of benzodiazepines can be depressogenic, and the resulting sedative effect could confound assessment of AD efficacy. An upper dose limit was enforced in the clinical trials, and patients were not to take benzodiazepines within 8 hours of intranasal dosing to reduce any potential impact on efficacy or safety assessments.
Included as missing information?	No
Rationale (if not included as missing information)	The exclusion criterion was implemented for the purpose of the clinical trials and not for a specific safety concern.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 16	**Major surgery (eg, requiring general anesthesia) within 12 weeks before the start of the trial, or subjects who have not fully recovered from surgery before the start of the trial**
Reason for being an exclusion criterion	Patients with history of major surgery were excluded from the clinical trials so as not to confound the assessment of safety.
Included as missing information?	No
Rationale (if not included as missing information)	The exclusion criterion was implemented for the purpose of the clinical trials and not for a specific safety concern. Except for patients with recent prior revascularization procedure (in whom an elevation of blood pressure could pose a serious risk), SPRAVATO may be used in patients who have had prior surgery. The safety profile in such patients is not expected to be different.
Criterion 17	**Severe renal impairment (CrCl <30 mL/min)**
Reason for being an exclusion criterion	Patients with severe renal impairment (CrCl <30 mL/min) were excluded from the Phase 3 clinical trials to reduce potential confounding of the assessment of safety.
Included as missing information?	No
Rationale (if not included as missing information)	No dose adjustment of SPRAVATO is necessary in patients with mild to severe renal impairment (SmPC Section 4.2, Posology and method of administration).
Criterion 18	**Neurodegenerative disorder (eg, Alzheimer's disease, vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment or MMSE <25 or <22 for those subjects with less than an equivalent of high school education**
Reason for being an exclusion criterion	Patients with neurodegenerative disease were excluded from Phase 3 clinical trials due to their potential vulnerability to an agent for which safety had not been fully characterized. Patients with mild cognitive impairment or a low MMSE score were excluded so as not to confound safety and efficacy assessments that include evaluations of cognitive performance.
Included as missing information?	No
Rationale (if not included as missing information)	Although such patients are more susceptible to CNS adverse effects of psychotropic drugs, the exclusion criterion was mainly implemented for the purpose of the clinical trials and not for a specific safety concern related to serious adverse clinical outcomes.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

The clinical development program was likely to detect adverse reactions following prolonged or cumulative exposure. Evaluation of the safety profile of esketamine nasal spray following longer exposure did not reveal any adverse reactions in addition to those previously identified. No new adverse reactions were identified with repeated dosing in the long-term trials compared to those seen in the short-term trials; adverse reactions were typically seen shortly after dosing and generally resolved the same day.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Although prohibited by protocol, exposure to esketamine during pregnancy occurred in the clinical development program. Across all completed and ongoing trials, 15 pregnancies were reported in female subjects who were exposed to esketamine.[a]
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with severe hepatic impairment were not included in the clinical development program. Esketamine was administered to 259 subjects with mild hepatic impairment and 4 subjects with moderate hepatic impairment in clinical trials.
• Patients with renal impairment	Patients with severe renal impairment (CrCl <30 mL/min) were not included in the Phase 3 clinical trials. Esketamine was administered to 296 subjects with mild renal impairment (CrCl 60 to <90 mL/min) and 45 subjects with moderate renal impairment (CrCl 30 to <60 mL/min) in clinical trials. Patients on dialysis were not studied.
• Patients with cardiovascular impairment	Not included in the clinical development program.
• Patients with psychiatric comorbidities	Not included in the clinical development program.
Population with relevant different ethnic origin	Of the 2,151 esketamine-treated subjects in the All Clinical Trials Population, 1,786 (83.0%) were white, 105 (4.9%) were black or African American, 159 (7.4%) were Asian, and 101 (4.7%) were of other or mixed racial background or ethnicity.
Pediatric patients	Not included in the adult clinical development program.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Elderly patients	Of the 2,151 esketamine-treated subjects in the All Clinical Trials Population, 197 (9.2%) were ≥65 years, 26 (1.2%) were ≥75 years, and 2 (0.1%) were ≥85 years.

[a:] Includes medically confirmed and blinded cases from all interventional clinical trials.

Table SIV.3: Summary of Safety Concerns Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Patient exposure was calculated using the dosage recommendations for TRD in the Company Core Data Sheet with an assumed dose of 56 mg of esketamine per treatment session. Based on the recommended dosing, the dose assumption is as follows:

- Weeks 1 to 4: Two treatment sessions per week with administration of 56 mg per treatment session, for a total of 448 mg.
- Weeks 5 to 8: One treatment session per week with administration of 56 mg per treatment session, for a total of 224 mg.
- Weeks 9 to 26: One treatment session every other week with administration of 56 mg per treatment session, for a total of 504 mg.

Assuming that the majority of patients are treated for 26 weeks or less, the total exposure would be 1176 mg. It is important to note that actual dosage and dosing frequency may be individualized to maintain remission/response.

SV.1.2. Exposure

Interval and cumulative exposure to esketamine worldwide are summarized in Tables SV.1 and SV.2, respectively.

Interval Exposure Estimates

Table SV.1: Interval Exposure to Esketamine (01 March 2022 to 28 February 2023)

Region	Country	Person-Years[a]
European Union	Austria	[redacted]
	Belgium	
	Croatia	
	Cyprus	
	Czechia	
	Denmark	
	Estonia	
	Finland	
	France	
	Germany	
	Greece	
	Hungary	
	Ireland	
	Italy	

Table SV.1: Interval Exposure to Esketamine (01 March 2022 to 28 February 2023)

Region	Country	Person-Years[a]
	Latvia	C
	Lithuania	C
	Netherlands	CC
	Poland	C
	Portugal	C
	Roumenia	C
	Slovakia	C
	Spain	CC
	Sweden	C
European Union Subtotal		CCI
North America	Canada	CC
	Mexico	C
	United States	CCI
North America Subtotal		CCI
Rest of World	Argentina	C
	Australia	CC
	Brazil	CC
	Chile	C
	Costa Rica	C
	Dominican Republic	C
	Ecuador	C
	Egypt	CC
	El Salvador	C
	Guadeloupe	C
	Honduras	C
	Hong Kong	C
	Indonesia	C
	Israel	CC
	Jordan	C
	Kuwait	C
	Malaysia	C
	Martinique	C
	Monaco	C
	Morocco	C
	Muskat Oman	C
	New Zealand	C
	Nicaragua	C
	Norway	C
	Panama	C
	Peru	C
	Philippines	C
	Reunion	C
	Saudi Arabia	CC
	Serbia	C
	Singapore	C
	South Africa	C
	South Korea	CC
	Switzerland	C
	Taiwan	C
	Turkey	C
	United Arab Emirates	CC
	United Kingdom	C

Table SV.1: Interval Exposure to Esketamine (01 March 2022 to 28 February 2023)

Region	Country	Person-Years[a]
Rest of World Subtotal		CCI
Worldwide Total		CCI

a: Assumption used for the current data is 1 person-year=1,176 mg.

Based on the CCI mg of esketamine distributed worldwide by the Company from 01 March 2022 to 28 February 2023, the estimated interval exposure is CCI PY.

Cumulative Exposure Estimates

Table SV.2: Cumulative Exposure to Esketamine (Launch to 28 February 2023)

Region	Country	Person-Years[a]
European Union	Austria	CC
	Belgium	CCI
	Croatia	CC
	Cyprus	C
	Czechia	C
	Denmark	C
	Estonia	C
	Finland	CC
	France	CCI
	Germany	CC
	Greece	C
	Hungary	C
	Ireland	C
	Italy	CC
	Latvia	C
	Lithuania	C
	Luxembourg	C
	Malta	C
	Netherlands	CC
	Poland	C
	Portugal	C
	Roumenia	C
	Slovakia	C
	Spain	CC
	Sweden	CC
	United Kingdom[b]	C
EU Subtotal		CCI
North America	Canada	CC
	Mexico	C
	United States	CCI
North America Subtotal		CCI
Rest of World	Argentina	C
	Australia	CC
	Brazil	CC
	Chile	C
	Costa Rica	C
	Dominican Republic	C
	Ecuador	C
	Egypt	CC

Table SV.2: Cumulative Exposure to Esketamine (Launch to 28 February 2023)

Region	Country	Person-Years[a]
	El Salvador	[redacted]
	Guadeloupe	[redacted]
	Honduras	[redacted]
	Hong Kong	[redacted]
	Iceland	[redacted]
	Indonesia	[redacted]
	Israel	[redacted]
	Jamaica	[redacted]
	Jordan	[redacted]
	Kazakhstan	[redacted]
	Kuwait	[redacted]
	Malaysia	[redacted]
	Martinique	[redacted]
	Miscellaneous Country	[redacted]
	Monaco	[redacted]
	Morocco	[redacted]
	Muskat Oman	[redacted]
	New Zealand	[redacted]
	Nicaragua	[redacted]
	Norway	[redacted]
	Panama	[redacted]
	Peru	[redacted]
	Philippines	[redacted]
	Qatar	[redacted]
	Reunion	[redacted]
	Saudi Arabia	[redacted]
	Serbia	[redacted]
	Singapore	[redacted]
	South Africa	[redacted]
	South Korea	[redacted]
	Switzerland	[redacted]
	Taiwan	[redacted]
	Turkey	[redacted]
	United Arab Emirates	[redacted]
	United Kingdom[b]	[redacted]
Rest of World Subtotal		[redacted]
Worldwide Total		[redacted]

a: Assumption used for the current data is 1 person year=1,176 mg.
b: United Kingdom is no longer a part of the European Union and has been grouped under rest of world from January 2021 onwards.

Based on the [redacted] mg of esketamine distributed worldwide by the Company since launch to 28 February 2023, the estimated exposure is [redacted] PY.

Additional Stratifications for Esketamine

Additional stratifications are provided using IQVIA (formerly IMS MIDAS™) data where possible and appropriate. Market research sources for nonstudy exposure data are unavailable for breakdowns such as usage in pregnant or breastfeeding women, usage in hepatic impairment population, and usage in renal impairment population.

Exposure by Age and Sex Presented as a Percentage of Prescription Sales

Prescription sales stratified by age and sex are available from IQVIA and are presented below (as a percentage of total prescriptions).

Further splits such as sex within age group are not provided since it is not appropriate to stratify to this level of detail based on prescription information available from IQVIA for these subcategories. Prescription units are reported as absolute values (see Tables SV.3, SV.4, and SV.5).

Table SV.3: Post-marketing (Nonstudy) Esketamine Exposure by Age Group in Europe (01 October 2019 to 30 September 2022)

Age Groups (Years)[a]	EU[b] (610 Prescriptions[c])
16 to 35	[redacted] %
36 to 65	[redacted] %

a: Regional prescription data by age were only available for the last 3 years ending September 2022.
b: Data stratified by age were only available in Italy.
c: Included retail channels

Table SV.4: Post-marketing (Nonstudy) Esketamine Exposure by Age Group Outside Europe (01 October 2019 to 30 September 2022)

Age Groups (Years)[a]	Non-EU[b] (16,066 Prescriptions[c])
0 to 15	[redacted] %
16 to 35	[redacted] %
36 to 65	[redacted] %
≥66	[redacted] %

a: Regional prescription data by age were only available for the last 3 years ending September 2022.
b: Data stratified by age were only available in the United States.
c: Included retail channels

Table SV.5: Post-marketing (Nonstudy) Esketamine Exposure by Sex (01 October 2019 to 30 September 2022)

Country	Females[a]	Males[a]
Italy ([redacted] prescriptions[b])	[redacted] %	[redacted] %
United States ([redacted] prescriptions[b])	[redacted] %	[redacted] %

a: Regional prescription data by sex were only available for the last 3 years ending September 2022. Data were only available for the Italy and the United States.
b: Included retail channels

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Drug abuse is an important identified risk for SPRAVATO.

The exact mechanism underlying esketamine's abuse potential is unknown. Esketamine is active within the CNS and has a mechanism of action similar to that of racemic ketamine. As antagonists of NMDARs, both ketamine and esketamine induce psychoactive effects. Ketamine is a known drug of abuse recreationally and induces psychological effects, including dissociation and other perceptual distortions; alterations in cognition; and changes in mood. The most common way that ketamine is used recreationally is insufflation.

Evidence from an esketamine abuse potential study suggests that its potential for abuse is similar to that of ketamine (Trial 54135419TRD1015).

The abuse potential of SPRAVATO and its mitigation are addressed in the EU PI (ie, SmPC and PL) and include the following concepts:

- SPRAVATO is administered under the direct supervision of an HCP.
- The recommended dosing frequency of SPRAVATO for the TRD indication is twice weekly for 4 weeks, followed by weekly or every-other-week dosing for patients with a favorable clinical response. During longer-term treatment, physicians are recommended to individualize the dosing frequency to the lowest frequency needed to maintain the patient's clinical response and to perform periodic re-evaluation of patients to determine the need for continued treatment. For the indication of acute short-term treatment of psychiatric emergency due to MDD, the recommended dosing frequency of SPRAVATO is twice weekly for 4 weeks.
- Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Physicians are advised to assess individuals prior to treatment for a history of substance use disorder and to monitor for signs of abuse or dependence.

SPRAVATO is designed with the following features to deter abuse and misuse:

1. The product is supplied in limited pack sizes.
2. The drug product is contained in a Type I glass vial sealed with a chlorobutyl rubber stopper. The filled and stoppered vial is assembled into a manually activated nasal spray device. The device is difficult to disassemble due to interlocking design features of the actuator subassembly. Attempts to break open the device damage the vial and the contents are lost. The force required to pull the device apart is at least 60 Newtons (~13 pounds). If the device is taken apart, the stoppered vial provides an additional challenge to disassembly, as it is very difficult to pull the stopper out. Breaking the vial instead results in loss of the contents.
3. The product is supplied as a single-use device containing a total of 32.3 mg of esketamine HCl (equivalent to 28 mg of esketamine). When manually actuated, the device dispenses 2 individual sprays; no sprays remain after the second spray is actuated.

4. The nasal spray device has a nominal fill volume of 230 µL and a delivery volume of 200 µL. The average measured residual volume left in the nasal spray device after actuation is ~30 µL (4 mg base).

Legal controls (eg, restrictions on storage and prescribing including special and restricted medical prescription with categorization at the Member State level) are in place according to local requirements in the majority of Member States where esketamine is scheduled, either directly or indirectly due to its chemical relationship to ketamine. In these Member States, the scheduling class is the same as that which applies to any ketamine- or esketamine-containing medicinal product. The following measures minimize the risk of abuse, diversion, and misuse:

- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- All treatment should be administered under the direct supervision of an HCP.
- HCPs are advised to monitor patients for signs of abuse or dependence.
- A Controlled Access Program has been implemented, a key element of which is to ensure SPRAVATO is dispensed to the healthcare settings where administration takes place, as agreed at the Member State level, based on local requirements and/or local healthcare systems.

Key messages regarding product administration and the potential for abuse and dependence are additional risk minimization measures. Details are provided in Part V.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Gastrointestinal effects including nausea and vomiting

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable

Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the routine risk minimization messages in the product information are considered adequate:

Transient dizziness and vertigo

Known risks that do not impact the risk-benefit profile:

Transient mental and cognitive impairment

Transient anxiety

Transient psychiatric and neurological effects, including tremor, dysarthria, hypoesthesia, lethargy, dysgeusia, and euphoric mood

Nasal effects including nasal discomfort, crust, pruritus, and dryness

Other reasons for considering the risks not important:

Respiratory depression

Respiratory depression is a known adverse reaction for marketed esketamine solution for injection/infusion and marketed ketamine solution for injection/infusion, the risk of which is dependent on dose (ie, overdosage) and speed of the intravenous injection (ie, overly rapid administration).

No clinically significant decreases in respiratory rate were observed in esketamine Phase 3 trials. No cases of respiratory depression were reported, and no subjects required resuscitation. Isolated cases of 2 or more consecutive oxygen saturation levels below 93% within the same visit (based on the pulse oximetry data) were not associated with clinical symptoms of compromised respiratory function and resolved spontaneously in the post-dose period prior to discharge, while vital signs remained within the normal range.

Suicidal ideation and behavior

Because suicidal ideation and behavior are symptoms of major depression and TRD, it is important to distinguish the contribution of treatment of these conditions to the risk of suicidal ideation and behavior from that of the underlying depression. The Applicant conducted a review to determine the occurrence of suicide-related events.

Across all Phase 2 and 3 esketamine trials, there was a trend towards a reduction in suicidal ideation and

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

behavior using the C-SSRS. Most subjects reported no suicidal ideation or behavior during these trials.

For subjects with no suicidal ideation or behavior at baseline, the rates of reported suicidal ideation (based on C-SSRS) occurring at least once during the treatment phase were similar for the esketamine + oral AD groups compared to the placebo + oral AD groups in the short-term double-blind trials (TRD3001/3002: 10.2% vs. 12.3%; TRD3005: 13.8% vs. 16.7%) and in the double-blind maintenance phase of the relapse prevention trial TRD3003 (2.4% vs. 4.5%).

Severe suicidality-related TEAEs, defined as PTs of Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, and Suicide attempt, were reported at a low incidence (<1% for individual PTs) in each of the Phase 2 and 3 trials that was below the background rates expected in the treated population. Clinical review of suicidality-related TEAEs indicated that most of these events were likely associated with the underlying disease.

Hepatobiliary disorders

Hepatobiliary disorders are known adverse reactions for marketed esketamine solution for injection/infusion and marketed ketamine solution for injection/infusion. Hepatotoxicity and cholangiopathy have been described in the literature for ketamine in the context of long-term use or high doses.

Esketamine nasal spray was studied in subjects with mild to moderate hepatic impairment (Trial ESKETINTRD1011). Following administration of a single 28 mg dose of esketamine nasal spray, mean total esketamine C_{max} and AUC were similar in subjects with mild hepatic impairment (Child Pugh class A) as compared to subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child Pugh class B), total esketamine C_{max} was approximately 8% higher as compared to subjects with normal hepatic function, whereas AUC_{last} and AUC_{∞} values were 114% and 103% higher, respectively.

There was no evidence of treatment-emergent hepatotoxicity associated with esketamine nasal spray. Across the completed Phase 2 and 3 trials in TRD, increases in ALT and/or AST of greater than 3 times the ULN occurred at low rates among the esketamine + oral AD treatment groups (ie, <2% in all trials/trial phases).

The observed increases in ALT/AST in the Phase 3 trials in TRD were primarily asymptomatic, transient, and resolved spontaneously without worsening while treatment with esketamine + oral AD continued. No persistent increases in liver transaminases were observed. A qualitative assessment of the individual cases showed that majority of the subjects with markedly elevated transaminases had an alternative etiology (eg, co-medications with known hepatotoxic effects, such as statins and acetaminophen; underlying disease, such as viral hepatitis B, fatty liver, or cholelithiasis; or history of excessive alcohol consumption).

Across all completed Phase 1, 2, and 3 trials with esketamine, no subject met the criteria for severe drug-induced hepatocellular injury as defined by Hy's law. Further, no cases of treatment-emergent elevated total serum bilirubin levels to >2×ULN were identified in esketamine-treated subjects.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Important Identified Risks	
Drug abuse	Significant clinical consequences of esketamine abuse include attenuation and dependence if the product is used outside the approved indication and/or dose limits. The observed low incidence of severe TEAEs suggestive of drug abuse and the lack of evidence of a distinct withdrawal syndrome after cessation of dosing based on PWC-20 scores suggest that the drug abuse potential for patients with TRD alone is low. Patients with comorbid TRD and substance abuse disorders have not been studied; therefore, the risk in this population is unknown. The available data from patients with TRD suggest no significant impact on the risk-benefit balance of esketamine nasal spray. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on the risk of abuse. Prescribers are advised that individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of esketamine nasal spray and that individuals should be assessed prior to treatment for a history of substance use disorder, including alcohol. Monitoring for signs of abuse or dependence is recommended.
Transient dissociative states and perception disorders	Given that dissociative states and perception disorders observed in the clinical trials were transient, self-limiting, and without clinically significant adverse outcomes, the overall impact on the risk-benefit balance of the product is considered low; however, the impact on an individual patient may be significant. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on the risk of dissociative states and perception disorders. A checklist for readiness to leave will be provided to aid HCPs in determining when a patient is deemed stable and can safely be allowed to leave following esketamine nasal spray administration.
Disturbances in consciousness	Although a sedative effect was consistently observed during the clinical development program, no severe consequences of somnolence and sedation have been reported in clinical trials. However, somnolence/sedation may potentially impact a patient's ability to drive or use machinery and may increase the patient's risk of accidents, falls, or dangerous behavior, particularly if patients are allowed to leave too soon after esketamine nasal spray administration. Therefore, the overall impact on the risk-benefit balance of the product is considered low to moderate. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on how to manage the risk. A checklist for readiness to leave will be provided to aid HCPs in determining when a patient is deemed stable and can safely be allowed to leave following esketamine nasal spray administration.

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Blood pressure increased	Due to the transient and self-limiting nature of the cardiovascular effects observed in clinical trials, the overall impact on the risk-benefit balance of the product is considered low; however, the impact on an individual patient may be significant. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on how to manage the risk. A checklist for readiness to leave will be provided to aid HCPs in determining when a patient is deemed stable and can safely be allowed to leave following esketamine nasal spray administration.
Important Potential Risks	
Cognitive disorders and memory impairment (long-term use)	Given the recommended intermittent dosing frequency for esketamine nasal spray, and considering that most events related to cognitive disorders and memory impairment following long-term use in clinical trials were neither severe nor serious, and were generally self-limiting and resolved without intervention, the impact on the risk-benefit balance of the product is expected to be low.
Interstitial cystitis (long-term use)	Interstitial cystitis is a serious adverse reaction that may result in persistent or significant disability or incapacity. Given that no cases of esketamine nasal spray-related interstitial cystitis were observed in any of the Phase 2 and Phase 3 trials, which involved treatment for up to 1 year, the impact on the risk-benefit balance of the product is expected to be low. With intermittent exposure at the doses of 28 mg, 56 mg, and 84 mg recommended in the SmPC for treatment of patients with TRD, the bladder has sufficient time between dosing sessions for self-repair from any potential irritation.
Missing Information	
Use during pregnancy	There are no or limited data on the use of esketamine in pregnant women. The possibility of neurotoxicity in developing fetuses cannot be excluded based on published findings suggesting developmental neurotoxicity of ketamine in animals. Esketamine nasal spray is not recommended during pregnancy and in women of childbearing potential not using contraception.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The important potential risks of Cognitive disorders and memory impairment (long-term use) and Interstitial cystitis (long-term use) are removed from the list of safety concerns based on a cumulative evaluation of data from esketamine clinical trials (including long-term safety data from 54135419TRD3008), postmarketing sources, and the published literature, the results of which do not support a causal association between long-term esketamine exposure and the development of cognitive disorders, memory impairment, or interstitial cystitis (Clinical Overview 2023).

Routine pharmacovigilance and risk minimization activities are sufficient to manage these risks.

Safety Concern	Reason for Removal
Cognitive disorders and memory impairment (long-term use)	Cognitive disorders and memory impairment (long-term use) was considered an important potential risk for esketamine based on published literature sources that reported cognitive disorders and memory impairment associated with long-term ketamine use and abuse. The effect of esketamine on cognitive functioning was evaluated in short-term Phase 2 and short- and long-term Phase 3 trials in adults with TRD, including the long-term safety study 54135419TRD3008; the results of these studies suggested that performance on cognitive tests was slightly improved or remained stable. Reviews of postmarketing data from the MAH's global safety database and the published literature identified no new safety information related to the development of cognitive disorders or memory impairment with long-term esketamine use. With the completion of 54135419TRD3008, all pharmacovigilance activities for this risk have been completed. Cognitive disorders and memory impairment will continue to be monitored through routine pharmacovigilance activities.
Interstitial cystitis (long-term use)	Interstitial cystitis (long-term use) was considered an important potential risk for esketamine based on published literature sources that reported interstitial cystitis and lower urinary tract symptoms in long-term street users of ketamine and at doses greater than 10 times therapeutic doses. No cases of esketamine-related interstitial cystitis were reported during the clinical development program, which involved long-term exposure to esketamine for up to 79 months in 54135419TRD3008. Reviews of postmarketing data from the MAH's global safety database and the published literature identified no new safety information related to interstitial cystitis with long-term esketamine use. With the completion of 54135419TRD3008, all pharmacovigilance activities for this risk have been completed. Interstitial cystitis will continue to be monitored through routine pharmacovigilance activities.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks:

- Drug abuse
- Transient dissociative states and perception disorders
- Disturbances in consciousness
- Blood pressure increased

Important potential risks:

- None

Missing information:

- None

The following MedDRA versions were used to classify the adverse event information from esketamine clinical trials:

- Version 18.0:
  - MDSI trial ESKETINSUI2001.
- Version 21.1:
  - MDSI trials 54135419SUI3001 and 54135419SUI3002.
- Version 25.1:
  - all TRD trials.

In the tables that follow (MDSI trials only), the esketamine 84 mg + SOC treatment group is presented as "Esketamine 84 mg".

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk – Drug Abuse

Potential Mechanisms:

Ketamine and esketamine are non-competitive, non-selective, open-channel NMDAR antagonists. As antagonists of NMDARs, ketamine and esketamine induce psychoactive effects. Ketamine is well known for its abuse potential in both humans and animals (Liu 2016). The exact mechanism underlying ketamine's abuse potential is unknown. Given the known direct targets of ketamine and the effects of other NMDAR antagonists in the same class, the behavioral effects of ketamine at subanesthetic doses, including perceptual/dissociative symptoms, are thought to be primarily driven by its activity at the NMDAR, although indirect actions on dopaminergic neurotransmission may contribute as well (Broadbear 2004; De Luca 2012; Shram 2011; Winger 2002).

Evidence Source(s) and Strength of Evidence:

Evidence from an esketamine abuse potential trial (Trial 54135419TRD1015) suggests that the potential for abuse is similar to that of ketamine, a known drug of abuse recreationally. No evidence of drug-seeking behavior was observed, and no confirmed cases of diversion were reported in clinical trials of esketamine nasal spray.

Characterization of the Risk - Data:

Table SVII.1a: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Treatment-emergent Adverse Events Suggestive of Drug Abuse in Clinical Trials (TRD)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD (N=571)	Placebo + Oral AD (N=486)	Esketamine + Oral AD (N=1889)
Frequency	n (%)	n (%)	n (%)
Subjects with TEAEs suggestive of drug abuse[a]	292 (51.1%)	62 (12.8%)	1184 (62.7%)
Odds ratio	7.2		
95% CI[b]	5.2 to 9.9		
Seriousness/outcomes of events[c]	478	85	2297
Fatal	0	0	0
Serious	0	1 (1.2%)	12 (0.5%)
Recovered	474 (99.2%)	83 (97.6%)	2263 (98.5%)
Recovered with sequelae	3 (0.6%)	0	5 (0.2%)
Recovering	1 (0.2%)	1 (1.2%)	8 (0.3%)
Not recovered	0	1 (1.2%)	20 (0.9%)
Unknown	0	0	0
Missing	0	0	1 (0.04%)
Severity of events[c]			
Mild	250 (52.3%)	63 (74.1%)	1175 (51.2%)
Moderate	195 (40.8%)	19 (22.4%)	947 (41.2%)
Severe	33 (6.9%)	3 (3.5%)	175 (7.6%)
Missing	0	0	0

MedDRA version 25.1 was used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'TEAEs Suggestive of Drug Abuse'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine + oral AD to placebo + oral AD for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'TEAEs Suggestive of Drug Abuse' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

The following trials are included in the All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg). The following trials are included in the All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg).

Note: Subjects in the All Randomized, Blinded Trials Population who were exposed to esketamine in trials ESKETINTRD3001 or ESKETINTRD3002 and transferred to ESKETINTRD3003 and were re-randomized to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomized, Blinded Trials Population who received both esketamine and placebo in ESKETINTRD2003 in the Double-blind Phase were counted in both treatment groups.

Note: The All Randomized, Blinded Trials Population includes the first 2 weeks of the Follow-up phases for each of the trials listed, except for ESKETINTRD2003; for ESKETINTRD2003, the Follow-up data are included only for those subjects that did not enter the Open-label Phase.

Source: Adapted from TSFAE01.

[tsfae01.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsfae01.sas] 10JUL2023, 13:45

Table SVII.1b: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Treatment-emergent Adverse Events Suggestive of Drug Abuse in Clinical Trials (MDSI)

	Esketamine 84 mg (N=262)	Placebo (N=256)
Frequency	n (%)	n (%)
Subjects with TEAEs suggestive of drug abuse[a]	170 (64.9%)	70 (27.3%)
Odds ratio	4.9	
95% CI[b]	3.3 to 7.3	
Seriousness/outcomes of events[c]	299	93
Fatal	0	0
Serious	0	2 (2.2%)
Recovered	296 (99.0%)	91 (97.8%)
Recovered with sequelae	0	0
Recovering	0	0
Not recovered	3 (1.0%)	2 (2.2%)
Unknown	0	0
Missing	0	0
Severity of events[c]		
Mild	173 (57.5%)	74 (79.6%)
Moderate	112 (37.2%)	17 (18.3%)
Severe	14 (4.7%)	2 (2.2%)
Missing	2 (0.7%)	0

MedDRA versions 18.0 (ESKETINSUI2001) and 21.1 (54135419SUI3001 and 54135419SUI3002) were used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Events Potentially Suggestive of Drug Abuse'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine to placebo for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Events Potentially Suggestive of Drug Abuse' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

The following trials are included in the All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

Note: The All Randomized, Blinded Trials Population includes the first 2 weeks of the Follow-up phases for each of the trials listed.

Source: Adapted from TSFAE01.

[TSFAE01.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSFAE01.SAS] 17MAY2019, 15:40

The search strategy and a list of PTs returned by the search for the important identified risk of Drug abuse is presented in Annex 7.3.

Characterization of the Risk - Discussion:

TRD

Data from all clinical trials of esketamine nasal spray were examined for the occurrence of CNS effects suggesting that the drug might be sought by patients specifically for abuse purposes. Such effects are related to esketamine's pharmacology and were identified prior to the start of the Phase 3 program based on the known properties of esketamine and ketamine. In a trial of abuse potential conducted in recreational polydrug users (n=41), single doses of esketamine nasal spray (84 mg and 112 mg) and of intravenous ketamine (positive control; 0.5 mg/kg infused over

40 minutes) produced significantly greater scores than placebo on subjective ratings of "drug liking" and other measures of subjective drug effects.

The frequency of reported TEAEs suggestive of drug abuse was 62.7% in the All Clinical Trials Population and 4.0 times higher in the esketamine + oral AD group vs. the placebo + oral AD group in the double-blind trials (51.1% vs. 12.8%). The OR of 7.2 (95% CI: 5.2, 9.9) indicated that the odds of a TEAE suggestive of drug abuse occurring in the esketamine + oral AD group were 7.2 times that of the placebo + oral AD group. In the double-blind trials, no fatal events were reported in either group, and only a single serious event was reported in the placebo + oral AD group vs. no cases in the esketamine + oral AD group. In the All Clinical Trials Population, 12 (0.5%) events were serious, and none was fatal. In the double-blind trials, 93.1% of the events were mild or moderate in severity, with 6.9% of the events being severe in the esketamine + oral AD group vs. 3.5% in the placebo + oral AD group. In the All Clinical Trials Population, 92.4% of the events were mild or moderate, and 7.6% of the events were severe. Across all trials of esketamine in TRD, TEAEs suggestive of drug abuse most commonly associated with esketamine were dizziness, dissociation, and somnolence. In the fixed-dose short-term trial, a higher incidence of dissociation was observed with the higher esketamine dose; the other commonly reported TEAEs suggestive of drug abuse did not show a dose effect. Across the TRD trials, the majority of TEAEs suggestive of drug abuse were transient and self-limiting, occurring and resolving on the day of dosing of esketamine nasal spray.

Dependence and attenuation have been reported with prolonged use of ketamine. Individuals who were using high doses on a frequent basis and considered dependent on ketamine reported withdrawal symptoms of cravings, anxiety, shaking, sweating, and palpitations.

The PWC-20 was administered in the TRD2003 trial and Phase 3 trials to assess potential withdrawal symptoms following cessation of esketamine nasal spray treatment. The categories of withdrawal symptom status were as follows: no symptom; improved; symptom present, unchanged; and new or worsened symptom. Across these trials, most subjects did not report symptoms on the PWC-20. Reported symptoms were primarily mild to moderate in severity. New or worsening symptoms that generally corresponded to worsening of depression occurred after withdrawal of treatment. Worsening of depression symptoms was observed mostly in subjects who discontinued treatment due to lack of therapeutic response. Across TRD trials, commonly reported symptoms following discontinuation of esketamine nasal spray were anxiety/nervousness, fatigue/lethargy/lack of energy, difficulty concentrating/remembering, dysphoric mood, depression, and irritability. In TRD trials including oral AD + placebo as a comparator, these same symptoms were also frequently reported by subjects following discontinuation of placebo. These reported symptoms were consistent with those of depression and anxiety. In the long-term maintenance Trial TRD3003, based on the PWC-20 results, there appeared to be no difference between treatment arms (ie, esketamine + oral AD vs. placebo + oral AD) for each of the 20 items, with no evidence suggestive of a distinct withdrawal syndrome.

MDSI

The frequency of reported TEAEs suggestive of drug abuse was 2.4 times higher in the esketamine + SOC group vs. the placebo + SOC group (64.9% vs. 27.3%). The OR of 4.9 (95% CI: 3.3, 7.3) indicated that the odds of a TEAE suggestive of drug abuse occurring in the esketamine + SOC group were 4.9 times that of the placebo + SOC group. No fatal events were reported in either group, and no serious events were reported in the esketamine + SOC group vs. 2 serious events in the placebo + SOC group. Of the events reported, 94.7% were mild or moderate in severity, and severe events made up 4.7% of events in the esketamine + SOC group vs. 2.2% in the placebo + SOC group. The most common TEAEs associated with esketamine suggestive of abuse potential were dizziness, dissociation, and somnolence. These symptoms were generally reported shortly after dosing on the day of esketamine administration and were transient and self-limiting. No new patterns were identified in the MDSI clinical trials compared with the TRD clinical trials.

Risk Factors and Risk Groups:

Risk factors and groups for substance abuse include mental health disorders (eg, depression, anxiety, and bipolar disorder), stressful environmental factors, taking addictive prescription medication, alcohol consumption, and family history of drug abuse and addiction.

Dependence and attenuation to SPRAVATO may develop, particularly when not used as prescribed (eg, taking high doses on a daily basis over an extended period of time) or in individuals with a history of drug abuse or dependence.

Preventability:

The decision to prescribe esketamine should be determined by a psychiatrist. SPRAVATO is available by special and restricted medical prescription only and administered under the direct supervision of an HCP. The risk for drug abuse is mitigated with appropriate warnings and instructions in the EU PI, limited pack sizes, and legal controls (eg, restrictions on storage and prescribing) according to local requirements in Member States where esketamine is scheduled. Additional risk minimization measures for this risk are described in Part V.2.

Impact on the Risk-benefit Balance of the Product:

Significant clinical consequences of SPRAVATO abuse include attenuation and dependence if the product is used outside the approved indications and/or dose limits. The observed low incidence of severe TEAEs suggestive of drug abuse and the lack of evidence of a distinct withdrawal syndrome after cessation of dosing based on PWC-20 scores suggest that the drug abuse potential for patients with TRD alone is low. Patients with comorbid TRD or MDSI and substance abuse disorders have not been studied; therefore, the risk in this population is unknown.

The available data from patients with TRD and MDSI suggest no significant impact on the risk-benefit balance of SPRAVATO.

Public Health Impact:

SPRAVATO is administered under the direct supervision of an HCP; therefore, the impact of drug abuse on public health is expected to be low.

Annex 1 MedDRA Term:

SMQ: Drug abuse, dependence and withdrawal (broad)

Important Identified Risk – Transient Dissociative States and Perception Disorders

Potential Mechanisms:

Transient dissociative states reflect a type of sensory or proprioceptive perceptual disorder and are expected effects of esketamine based on its mechanism of action as a non-competitive, non-selective, open-channel NMDAR antagonist. The perceptual side effects attenuate with repeated administration and intensify with higher doses (within the subanesthetic dose range), while the AD action is maintained or improves over repeated treatments and appears to reach maximum AD effect at an intravenous ketamine dose of 0.5 mg/kg (Fava 2017), an intravenous esketamine dose of 0.2 mg/kg (TRD2001), and an intranasal esketamine dose of 84 mg (TRD3001 data). Moreover, the perceptual/dissociative side effects do not correlate with improvement of depression symptoms (Fava 2017; TRD3001 and TRD3002 data). Additionally, there was insufficient evidence from mediation analyses on data collected in Trial TRD3002 that the AD effect of esketamine nasal spray (assessed by change in MADRS after initiation of the first dose and after the last dose) was mediated by the perceptual/dissociative effects (assessed by change in CADSS total scores 40 minutes postdose). These findings suggest that distinct mechanisms may underlie the AD and perceptual actions. These mechanisms may depend on different subtypes of NMDARs.

Evidence Source(s) and Strength of Evidence:

Transient dissociative states and perception disorders are expected effects of SPRAVATO based on esketamine’s mechanism of action, and have been observed in all phases of the clinical development program.

Characterization of the Risk - Data:

Table SVII.2a: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Dissociative States/Perception Disorders-related Events in Clinical Trials (TRD)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD (N=571)	Placebo + Oral AD (N=486)	Esketamine + Oral AD (N=1889)
Frequency	n (%)	n (%)	n (%)
Subjects with dissociative states/perception disorders-related events[a]	154 (27.0%)	15 (3.1%)	669 (35.4%)
Odds ratio	11.6		
95% CI[b]	6.7 to 21.5		
Seriousness/outcomes of events[c]	184	16	845
Fatal	0	0	0
Serious	0	0	0
Recovered	181 (98.4%)	16 (100.0%)	839 (99.3%)
Recovered with sequelae	3 (1.6%)	0	2 (0.2%)
Recovering	0	0	1 (0.1%)
Not recovered	0	0	2 (0.2%)
Unknown	0	0	0
Missing	0	0	1 (0.1%)
Severity of events[c]			
Mild	85 (46.2%)	13 (81.3%)	406 (48.0%)
Moderate	85 (46.2%)	3 (18.8%)	362 (42.8%)
Severe	14 (7.6%)	0	76 (9.0%)
Missing	0	0	1 (0.1%)

MedDRA version 25.1 was used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Dissociative States/Perception Disorders-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine + oral AD to placebo + oral AD for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Dissociative States/Perception Disorders-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

The following trials are included in the All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg). The following trials are included in the All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg).

Note: Subjects in the All Randomized, Blinded Trials Population who were exposed to esketamine in trials ESKETINTRD3001 or ESKETINTRD3002 and transferred to ESKETINTRD3003 and were re-randomized to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomized, Blinded Trials Population who received both esketamine and placebo in ESKETINTRD2003 in the Double-blind Phase were counted in both treatment groups.

Source: Adapted from TSFAE07.

[tsfae07.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsfae07.sas] 10JUL2023, 13:45

Table SVII.2b: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Dissociative States/Perception Disorders-related Events in Clinical Trials (MDSI)

	Esketamine 84 mg (N=262)	Placebo (N=256)
Frequency		
Subjects with dissociative states/ perception disorders-related events[a]	105 (40.1%)	21 (8.2%)
Odds ratio	7.5	
95% CI[b]	4.4 to 13.1	
Seriousness/outcomes of events[c]	130	21
Fatal	0	0
Serious	1 (0.8%)	0
Recovered	130 (100.0%)	21 (100.0%)
Recovered with sequelae	0	0
Recovering	0	0
Not recovered	0	0
Unknown	0	0
Missing	0	0
Severity of events[c]		
Mild	55 (42.0%)	18 (85.7%)
Moderate	61 (46.6%)	2 (9.5%)
Severe	14 (10.7%)	1 (4.8%)
Missing	1 (0.8%)	0

MedDRA versions 18.0 (ESKETINSUI2001) and 21.1 (54135419SUI3001 and 54135419SUI3002) were used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Dissociative States/Perception Disorders-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine to placebo for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Dissociative States/Perception Disorders-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

Note: The following trials are included in the All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

Source: Adapted from TSFAE02.

[TSFAE02.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSFAE02.SAS] 17MAY2019, 15:41

The search strategy and a list of PTs returned by the search for the important identified risk of Transient dissociative states and perception disorder is presented in Annex 7.3.

Characterization of the Risk - Discussion:

TRD

The frequency of reported AEs related to dissociative states/perception disorders was 35.4% in the All Clinical Trials Population and 8.7 times higher in the esketamine + oral AD group vs. the placebo + oral AD group in the double-blind trials (27.0% vs. 3.1%). The OR (95% CI) of 11.6 (6.7, 21.5) indicated that the odds of a dissociative states/perception disorders-related TEAE occurring in the esketamine + oral AD group were 11.6 times that of the placebo + oral AD group. In the double-blind trials, no fatal or serious events were reported in either group. No fatal or serious events were reported in the All Clinical Trials Population. In the double-blind trials,

92.3% of the events were mild or moderate in severity, with 7.6% of the events being severe in the esketamine + oral AD group vs. none in the placebo + oral AD group. In the All Clinical Trials Population, 90.9% of the events were mild or moderate, and 9.0% of the events were severe. In the All Clinical Trials Population, an outcome of "Recovered" was reported for 839 (99.3%) events, and an outcome of "Recovered with sequelae" was reported for 2 (0.2%) events.

Across completed Phase 2 and Phase 3 trials in TRD, the most common psychological effects of esketamine nasal spray, as captured using the CADSS, were dissociative states/perception disorders (including distortion of time and space and illusions), derealization, and depersonalization. Changes in mean CADSS score indicated that the onset of dissociative states/perception disorders generally occurred shortly after the start of the dose, peaked by 40 minutes postdose, and resolved by 1.5 hours postdose.

Transient dissociative states/perception disorders (based on the CADSS scores, overall TEAE incidence rates, and severe TEAE incidence rates) were more pronounced in subjects receiving higher doses of esketamine nasal spray.

Across the completed Phase 2 and Phase 3 TRD trials, the peak mean CADSS total score at the 40-minute timepoint in subjects treated with esketamine nasal spray decreased with consecutive doses. This attenuation of dissociative states/perception disorders was reflected in the changes in mean CADSS total score and mean component scores in the short-term trials in adults and elderly subjects, the relapse prevention trial, and the long-term safety trial. Consistent with CADSS findings, rates of the TEAEs of dissociation and perceptual effects and of the AEs of "feeling abnormal" and "feeling drunk" decreased with subsequent intranasal dosing sessions in the pooled short-term trials. A pharmacokinetics/pharmacodynamics model also showed an attenuation of the dissociative effects of esketamine nasal spray over the initial 4 weeks of treatment.

MDSI

The frequency of reported TEAEs related to dissociative states/perception disorders was 4.9 times higher in the esketamine + SOC group vs. the placebo + SOC group (40.1% vs. 8.2%). The OR of 7.5 (95% CI: 4.4, 13.1) indicated that the odds of a TEAE related to dissociative states/perception disorders occurring in the esketamine + SOC group were 7.5 times that of the placebo + SOC group. No fatal events were reported in either group, and only 1 serious event was reported in the esketamine + SOC group vs. none in the placebo + SOC group. Of the events reported, 88.6% were mild or moderate in severity, and 10.7% were severe in the esketamine + SOC group vs. 4.8% in the placebo + SOC group. The outcome was reported as "Recovered" for all events in both groups. Similar event characteristics (transient and generally occurring on the day of dosing) were observed in the MDSI clinical trials compared to the TRD clinical trials and no new patterns were identified.

<u>Risk Factors and Risk Groups:</u>

Risk factors for transient dissociative states and perception disorders are unknown.

There is a dose-response relationship between the esketamine dose and the severity of transient dissociative states/perception disorders, which is attenuated with repeated doses.

Preventability:

The decision to prescribe esketamine should be determined by a psychiatrist. SPRAVATO is available by special and restricted medical prescription only and is administered under the direct supervision of an HCP. Serious outcomes of dissociative states/perception disorders may be minimized by advising HCPs and patients about expected transient states/perception disorders, by advising HCPs about monitoring patients postdose until the patient is considered stable based on clinical judgement, and by advising patients not to drive or operate machinery until the day after treatment, following a restful sleep. Additional risk minimization measures for this risk are described in Part V.2.

Impact on the Risk-benefit Balance of the Product:

Given that dissociative states/perception disorders observed in the clinical trials were transient, self-limiting, and without clinically significant adverse outcomes, the overall impact on the risk-benefit balance of the product is considered low; however, the impact on an individual patient may be significant.

Public Health Impact:

The risk of transient dissociative states/perception disorders is managed through guidance provided in the EU PI, the Healthcare Professional Guide, the Patient Guide, and the Healthcare Professional Checklist; therefore, the impact of transient dissociative states/perception disorders on public health is expected to be low.

Annex 1 MedDRA Term:

HLT: Dissociative states

Important Identified Risk – Disturbances in Consciousness

Potential Mechanisms:

At AD doses, the side effects that follow administration of SPRAVATO, including sedation, are induced by primary or secondary actions of NMDAR antagonism, which is why these symptoms diminish rapidly with the decline in esketamine plasma levels.

However, unlike dissociation and AD responses, the sedative responses are variable from time to time in the same individual, suggesting that there are confounding factors that are not fully understood. An important mechanism for some of the outlying sedation effects was concomitant benzodiazepine use; thus, the addition of concomitant medications needs to be considered in the mechanism for the observed sedation. From the pharmacological target point of view, sedation might require directly engaging potassium/sodium HCN channels by ketamine or esketamine and/or γ-amino butyric acid stimulation from other sources. There is convincing evidence of the involvement of HCN in the sedation effects of ketamine and esketamine at higher concentrations.

Evidence Source(s) and Strength of Evidence:

Disturbances in consciousness such as sedation and somnolence are expected effects of SPRAVATO based on esketamine's mechanism of action, and have been observed in all phases of the clinical development program.

Characterization of the Risk - Data:

Table SVII.3a: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Disturbances in Consciousness-related Events in Clinical Trials (TRD)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD (N=571)	Placebo + Oral AD (N=486)	Esketamine + Oral AD (N=1889)
Frequency	n (%)	n (%)	n (%)
Subjects with disturbances in consciousness-related events[a]	124 (21.7%)	36 (7.4%)	627 (33.2%)
Odds ratio	3.5		
95% CI[b]	2.3 to 5.3		
Seriousness/outcomes of events[c]	135	38	753
Fatal	0	0	0
Serious	0	0	2 (0.3%)
Recovered	134 (99.3%)	37 (97.4%)	743 (98.7%)
Recovered with sequelae	0	0	1 (0.1%)
Recovering	0	0	3 (0.4%)
Not recovered	1 (0.7%)	1 (2.6%)	6 (0.8%)
Unknown	0	0	0
Missing	0	0	0
Severity of events[c]			
Mild	71 (52.6%)	27 (71.1%)	401 (53.3%)
Moderate	57 (42.2%)	10 (26.3%)	307 (40.8%)
Severe	7 (5.2%)	1 (2.6%)	45 (6.0%)
Missing	0	0	0

MedDRA version 25.1 was used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Disturbances in Consciousness-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine + oral AD to placebo + oral AD for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Disturbances in Consciousness-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

The following trials are included in the All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg). The following trials are included in the All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg).

Note: Subjects in the All Randomized, Blinded Trials Population who were exposed to esketamine in trials ESKETINTRD3001 or ESKETINTRD3002 and transferred to ESKETINTRD3003 and were re-randomized to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomized, Blinded Trials Population who received both esketamine and placebo in ESKETINTRD2003 in the Double-blind Phase were counted in both treatment groups.

Source: Adapted from TSFAE08.

[tsfae08.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsfae08.sas] 10JUL2023, 13:45

Table SVII.3b: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Disturbances in Consciousness-related Events in Clinical Trials (MDSI)

	Esketamine 84 mg (N=262)	Placebo (N=256)
Frequency		
Subjects with disturbance in consciousness-related events[a]	77 (29.4%)	32 (12.5%)
Odds ratio	2.9	
95% CI[b]	1.8 to 4.8	
Seriousness/outcomes of events[c]	85	34
Fatal	0	0
Serious	0	0
Recovered	85 (100.0%)	33 (97.1%)
Recovered with sequelae	0	0
Recovering	0	0
Not recovered	0	1 (2.9%)
Unknown	0	0
Missing	0	0
Severity of events[c]		
Mild	54 (63.5%)	28 (82.4%)
Moderate	30 (35.3%)	6 (17.6%)
Severe	1 (1.2%)	0
Missing	0	0

MedDRA versions 18.0 (ESKETINSUI2001) and 21.1 (54135419SUI3001 and 54135419SUI3002) were used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Disturbance in Consciousness-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine to placebo for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Disturbance in Consciousness-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

Note: The following trials are included in the All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

Source: Adapted from TSFAE07.

[TSFAE07.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSFAE07.SAS] 17MAY2019, 15:41

The search strategy and a list of PTs returned by the search for the important identified risk of Disturbances in consciousness is presented in Annex 7.3.

Characterization of the Risk - Discussion:

TRD

The frequency of reported AEs related to disturbances in consciousness was 33.2% in the All Clinical Trials Population and 2.9 times higher in the esketamine + oral AD group vs. the placebo + oral AD group in the double-blind trials (21.7% vs. 7.4%). The OR (95% CI) of 3.5 (2.3, 5.3) indicated that the odds of a disturbance in consciousness-related TEAE occurring in the esketamine + oral AD group were 3.5 times that of the placebo + oral AD group. In the double-blind trials, no fatal or serious events were reported in either group. In the All Clinical Trials Population, 2 (0.3%) events were reported to be serious, and none was fatal. In the double-blind trials, 94.8% of the events were mild or moderate in severity, with 5.2% of the events being severe

in the esketamine + oral AD group vs. 2.6% in the placebo + oral AD group. In the All Clinical Trials Population, 94.0% of the events were mild or moderate, and 6.0% of the events were severe. In the All Clinical Trials Population, an outcome of "Recovered", "Recovered with sequelae", or "Recovering" was reported for 747 (99.2%) events, and an outcome of "Not recovered" was reported for 6 (0.8%) events.

Most (>96%) reported TEAEs of somnolence or sedation occurred on the day of dosing in the short-term and long-term Phase 3 trials/trial phases in TRD and of these, ≥95% resolved spontaneously the same day. The frequency of TEAEs of somnolence reported on each dosing day was relatively stable across time.

Based on the pattern of responses on the MOAA/S in the Phase 2 and 3 trials in TRD, sedative effects of esketamine were generally mild, had an onset shortly after the nasal spray dosing peaking at 30 to 45 minutes postdose, and typically resolved by 1 to 1.5 hours postdose. Among esketamine treatment groups, 10% or fewer subjects across the Phase 3 trials/trial phases in TRD had an MOAA/S score of 3 or less (corresponding to moderate or greater sedation) on a dosing day, although the occurrence of these scores was higher than that for the oral AD + placebo group. Across the Phase 3 trials in TRD, 10 of the 1,601 subjects treated with esketamine + oral AD (and 1 of the 432 subjects who received oral AD + placebo), had an MOAA/S score of 0 (no reaction to painful stimulus [trapezius squeeze]) and/or 1 (response to trapezius squeeze, including purposeful and reflexive withdrawal). These isolated instances of severe sedation generally did not repeat with subsequent dosing.

MDSI

The frequency of reported TEAEs related to disturbances in consciousness was 2.4 times higher in the esketamine + SOC group vs. the placebo + SOC group (29.4% vs. 12.5%). The OR of 2.9 (95% CI: 1.8, 4.8) indicated that the odds of a TEAE related to disturbances in consciousness occurring in the esketamine + SOC group were 2.9 times that of the placebo + SOC group. No fatal or serious events were reported in either group. Of the events reported, 98.8% were mild or moderate in severity, and 1.2% was severe in the esketamine + SOC group vs. none in the placebo + SOC group. The outcome was reported as "Recovered" for all events in the esketamine + SOC group vs. 97.1% of events in the placebo + SOC group.

Sedation was measured objectively using the MOAA/S scale and also evaluated based on TEAE reporting. Based on the MOAA/S, sedative effects were generally mild, had an onset shortly after the start of dosing, and typically resolved by 1 to 1.5 hours postdose. The TEAEs of somnolence and sedation occurred on the day of intranasal dosing and resolved spontaneously the same day. Discontinuations due to somnolence and sedation occurred in isolated cases in the Phase 2 and Phase 3 MDSI trials. In the cases of sedation, no symptoms of respiratory distress were observed, and vital signs and oxygen saturation remained within normal ranges. No new patterns were identified in the MDSI clinical trials compared with the TRD clinical trials.

<u>Risk Factors and Risk Groups:</u>

Risk factors for sedation include old age (elderly patients) and use of concomitant sedatives.

Preventability:

The decision to prescribe esketamine should be determined by a psychiatrist. Serious outcomes resulting from disturbances in consciousness may be minimized by advising HCPs and patients about expected disturbances in consciousness (ie, sedation, somnolence), monitoring patients postdose until patients are considered stable based on clinical judgement, and advising patients not to drive or operate machinery until the day after treatment, following a restful sleep. Additional risk minimization measures for this risk are described in Part V.2.

Impact on the Risk-benefit Balance of the Product:

Although a sedative effect was consistently observed during the clinical development program, no severe consequences of somnolence and sedation have been reported in clinical trials. However, somnolence/sedation may impact a patient's ability to drive or use machinery and may increase the patient's risk of accidents, falls, or dangerous behavior, particularly if patients are allowed to leave too soon after SPRAVATO administration. Therefore, the overall impact on the risk-benefit balance of the product is considered low to moderate.

Public Health Impact:

The risk of disturbances in consciousness (somnolence and sedation) is minimized by guidance provided in the EU PI and additional risk minimization materials; therefore, the impact of disturbances in consciousness on public health is expected to be low.

Annex 1 MedDRA Term:

HLT: Disturbances in consciousness

Important Identified Risk – Blood Pressure Increased

Potential Mechanisms:

Cardiovascular effects of ketamine and esketamine at subanesthetic doses include transient increases in blood pressure in some subjects. The primary target of both agents at such doses is NMDARs. In addition to producing a transient increase in glutamate release in the brain, a single administration of ketamine at subanesthetic doses increases dopamine and norepinephrine in several brain regions. These effects can be explained by their direct inhibition of interneurons through NMDARs. One plausible explanation for their cardiovascular side effects is that, through inhibition of interneurons directly, these agents stimulate excitatory neurons and catecholaminergic neurons, resulting in increased sympathetic nervous system activity.

Evidence Source(s) and Strength of Evidence:

Cardiovascular effects due to increased blood pressure are expected for SPRAVATO based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the CNS that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure, as well as cardiovascular and blood pressure-related events, in association with esketamine nasal spray have been reported in the completed randomized, double-blind, controlled and open-label clinical trials. In clinical trials, elevations of blood pressure were transient, generally self-limiting, and did not require intervention.

Characterization of the Risk - Data:

Table SVII.4a: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Increased Blood Pressure-related Events in Clinical Trials (TRD)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD (N=571)	Placebo + Oral AD (N=486)	Esketamine + Oral AD (N=1889)
Frequency	n (%)	n (%)	n (%)
Subjects with increased blood pressure-related events[a]	66 (11.6%)	19 (3.9%)	388 (20.5%)
Odds ratio	3.2		
95% CI[b]	1.9 to 5.8		
Seriousness/outcomes of events[c]	72	19	497
Fatal	0	0	0
Serious	1 (1.4%)	0	4 (0.8%)
Recovered	65 (90.3%)	19 (100.0%)	433 (87.1%)
Recovered with sequelae	2 (2.8%)	0	3 (0.6%)
Recovering	1 (1.4%)	0	22 (4.4%)
Not recovered	4 (5.6%)	0	38 (7.6%)
Unknown	0	0	0
Missing	0	0	1 (0.2%)
Severity of events[c]			
Mild	51 (70.8%)	15 (78.9%)	313 (63.0%)
Moderate	20 (27.8%)	4 (21.1%)	176 (35.4%)
Severe	1 (1.4%)	0	7 (1.4%)
Missing	0	0	1 (0.2%)

MedDRA version 25.1 was used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Increased Blood Pressure-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine + oral AD to placebo + oral AD for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Increased Blood Pressure-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

The following trials are included in the All Randomized, Blinded Trials Population: ESKETINTRD3001 (Double-blind Phase), ESKETINTRD3002 (Double-blind Phase), ESKETINTRD3003 (Double-blind Maintenance Phase), ESKETINTRD3005 (Double-blind Phase), and ESKETINTRD2003 (Double-blind Phase excluding esketamine 14 mg). The following trials are included in the All Clinical Trials Population: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, 54135419TRD3008, and ESKETINTRD2003 (excluding Double-blind Phase esketamine 14 mg).

Note: Subjects in the All Randomized, Blinded Trials Population who were exposed to esketamine in trials ESKETINTRD3001 or ESKETINTRD3002 and transferred to ESKETINTRD3003 and were re-randomized to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomized, Blinded Trials Population who received both esketamine and placebo in ESKETINTRD2003 in the Double-blind Phase were counted in both treatment groups.

Source: Adapted from TSFAE02.

[tsfae02.rtf] [jnj-54135419/z_rmp/dbr_rmp2023/re_rmp_trd/tsfae02.sas] 10JUL2023, 13:45

Table SVII.4b: Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Increased Blood Pressure-related Events in Clinical Trials (MDSI)

	Esketamine 84 mg (N=262)	Placebo (N=256)
Frequency		
Subjects with increased blood pressure-related events[a]	36 (13.7%)	15 (5.9%)
Odds ratio	2.6	
95% CI[b]	1.3 to 5.2	
Seriousness/outcomes of events[c]	45	17
Fatal	0	0
Serious	0	0
Recovered	45 (100.0%)	16 (94.1%)
Recovered with sequelae	0	0
Recovering	0	0
Not recovered	0	1 (5.9%)
Unknown	0	0
Missing	0	0
Severity of events[c]		
Mild	29 (64.4%)	15 (88.2%)
Moderate	11 (24.4%)	2 (11.8%)
Severe	5 (11.1%)	0
Missing	0	0

MedDRA versions 18.0 (ESKETINSUI2001) and 21.1 (54135419SUI3001 and 54135419SUI3002) were used to classify the adverse event information that is summarized in this table.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Increased Blood Pressure-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine to placebo for All Randomized, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Increased Blood Pressure-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarized.

Note: The following trials are included in the All Randomized, Blinded Trials Population: ESKETINSUI2001, 54135419SUI3001 and 54135419SUI3002 (Double-blind Phase for all trials).

Source: Adapted from TSFAE03.

[TSFAE03.RTF] [JNJ-54135419\Z_RMP\DBR_RMP2019\RE_RMP_SUI\PROD\TSFAE03.SAS] 17MAY2019, 15:41

The search strategy and a list of PTs returned by the search for the important identified risk of Blood pressure increased is presented in Annex 7.3.

Characterization of the Risk - Discussion:

TRD

The frequency of reported AEs related to increased blood pressure was 20.5% in the All Clinical Trials Population and 3.0 times higher in the esketamine + oral AD group vs. the placebo + oral AD group in the double-blind trials (11.6% vs. 3.9%). The OR (95% CI) of 3.2 (1.9, 5.8) indicated that the odds of an event related to increased blood pressure occurring in the esketamine + oral AD group were 3.2 times that of the placebo + oral AD group. In the double-blind trials, no fatal events were reported in either group; 1 serious event was reported in the esketamine + oral AD group vs. no events in the placebo + oral AD group. In the All Clinical Trials Population, 4 (0.8%) events

were reported to be serious, and none was fatal. In the double-blind trials, 98.6% of the events were mild or moderate in severity, with 1.4% of the events being severe in the esketamine + oral AD group vs none in the placebo + oral AD group. In the All Clinical Trials Population, 98.4% of the events were mild or moderate, and 1.4% of the events were severe.

Transient increases in SBP and DBP were observed shortly after esketamine nasal spray administration, reaching maximum within 40 minutes, at the time of peak plasma esketamine levels, and generally returning to values close to pre-treatment within 1.5 hours after administration. Reported increases in blood pressure were primarily asymptomatic. Most of the TEAEs associated with elevated blood pressure were transient and mild or moderate in severity. The largest mean maximum blood pressure increases across all intranasal dosing days compared with predose values in the total esketamine + oral AD group in pooled short-term trials (TRD3001 and TRD3002) were 13.3 mm Hg (SBP) and 8.7 mm Hg (DBP), compared with the corresponding blood pressure increases of 6.1 mm Hg (SBP) and 4.9 mm Hg (DBP) in subjects receiving placebo + oral AD.

Markedly abnormal blood pressure elevations (defined as SBP of at least 180 mm Hg and/or DBP of at least 110 mm Hg, and categorized per trial criteria as acute hypertension) were reported at rates ranging from 2.0% to 11.1% across Phase 3 trials in TRD. These occurred primarily within 1.5 hours after dosing. These markedly abnormal blood pressure increases were reported at higher rates in subjects with a history of hypertension as compared to subjects without a history of hypertension (pooled TRD3001/3002 trials: 7.6% vs. 4.3%; long-term safety Trial TRD3004: 7.3% vs. 2.9%; relapse-prevention trial TRD3003 [any phase]: 5.5% vs. 4.1%). In the short-term trials, markedly abnormal blood pressure increases occurred at a higher rate in elderly subjects vs. younger adults (11.1% vs. 4.9%).

MDSI

The frequency of reported TEAEs related to increased blood pressure was 2.3 times higher in the esketamine + SOC group vs. the placebo + SOC group (13.7% vs. 5.9%). The OR of 2.6 (95% CI: 1.3, 5.2) indicated that the odds of a TEAE related to increased blood pressure occurring in the esketamine + SOC group were 2.6 times that of the placebo + SOC group. No fatal or serious events were reported in either group. Of the events reported, 88.8% were mild or moderate in severity, and 11.1% were severe in the esketamine + SOC group vs. none in the placebo + SOC group. The outcome was reported as “Recovered” for all events in the esketamine + SOC group vs. 94.1% of events in the placebo + SOC group. No new patterns were identified in the MDSI clinical trials compared to the TRD clinical trials.

Risk Factors and Risk Groups:

The risk of cardiovascular effects is greater in patients for whom an increase in blood pressure poses a serious risk, for example:

- Patients who recently experienced a cardiovascular event, including myocardial infarction;

- Patients with aneurysmal vascular disease (including intracranial, thoracic aorta, abdominal aorta, or peripheral arterial vessels);
- Patients with history of intracerebral hemorrhage.

Preventability:

The decision to prescribe esketamine should be determined by a psychiatrist. SPRAVATO should not be administered to patients for whom blood pressure elevation poses a serious risk. To reduce the risk of blood pressure-related events, blood pressure should be monitored at each dosing session, predose and postdose. Postdose monitoring should be performed by HCPs with training in blood pressure monitoring.

Blood pressure monitoring equipment is required at each clinic/facility where SPRAVATO is administered.

Predose thresholds and recommendations regarding blood pressure assessments and actions to manage blood pressure elevation are provided in the SmPC.

Additional risk minimization measures for this risk are described in Part V.2.

Impact on the Risk-benefit Balance of the Product:

Due to the transient and self-limiting nature of the cardiovascular effects observed in clinical trials, the overall impact of increased blood pressure on the risk-benefit balance of SPRAVATO is considered low; however, the impact on an individual patient may be significant.

Public Health Impact:

SPRAVATO administration takes place under the direct supervision of an HCP; therefore, the impact of blood pressure increased on public health is expected to be low.

Annex 1 MedDRA Term:

PT: Blood pressure increased

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Drug abuse
	Transient dissociative states and perception disorders
	Disturbances in consciousness
	Blood pressure increased
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires

Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
Cumulative review of drug abuse-related serious adverse reactions in the PBRER/PSUR.	• To provide a standardized evaluation of this safety concern. • To further characterize the impact of drug abuse on the safety profile of SPRAVATO. • To improve patient management.	End of each PBRER/PSUR reporting interval.
Cumulative review (at an aggregate level) of serious adverse reactions related to the following safety concerns in the PBRER/PSUR: Transient dissociative states and perception disorders, Disturbances in consciousness, and Blood pressure increased.	• To provide a standardized evaluation of these safety concerns. • To further characterize the impact of these safety concerns on the safety profile of SPRAVATO. • To improve patient management.	End of each PBRER/PSUR reporting interval.

III.2. Additional Pharmacovigilance Activities

Study name and title	PCSNSP002812: Survey to Assess the Effectiveness of SPRAVATO Educational Materials for Additional Risk Minimization Measures in the European Union
Rationale and study objectives	To assess the effectiveness of additional risk minimization materials (ie, Healthcare Professional Guide, Patient Guide, Healthcare Professional Checklist) related to the understanding of the important identified risks of Drug abuse, Transient dissociative states and perception disorders, Disturbances in consciousness, and Blood pressure increased. A survey of HCPs involved in the prescription, administration, and management of SPRAVATO and of patients who use SPRAVATO is being conducted to assess knowledge and understanding of the following: • the appropriate patient age and level of severity of MDD for consideration of SPRAVATO use. • important identified risks of SPRAVATO. • monitoring considerations before and after SPRAVATO administration. • healthcare facility requirements for patient monitoring.
Safety concern(s) addressed	• Drug abuse • Transient dissociative states and perception disorders • Disturbances in consciousness • Blood pressure increased
Study design	A survey of HCPs is being conducted to measure the effectiveness of the materials to minimize the important identified risks associated with esketamine treatment. Sampled HCPs involved in the prescription, administration and management of esketamine treatment are asked to participate in the survey to assess knowledge and understanding of how to reduce important identified risks, in accordance with the educational materials. Observational cross-sectional study (survey).
Study population	HCPs involved in the prescription, administration, and management of SPRAVATO treatment and patients who use SPRAVATO.
Milestones	Protocol submission (initial): 23 June 2020 Conduct of survey (wave 1): within 4 years of availability of the approved materials in selected countries. Conduct of survey (wave 2): within 4 to 5 years of availability of the approved materials in selected countries. A report on the educational activities undertaken and the results of the survey will be submitted within 4 years and no later than 5 years after launch. Updates will also be reported in the PBRER/PSUR. Final report: 4Q 2024

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
PCSNSP002812: Survey to Assess the Effectiveness of SPRAVATO Educational Materials for Additional Risk Minimization Measures in the European Union *Ongoing*	To assess the effectiveness of additional risk minimization materials (ie, Healthcare Professional Guide, Patient Guide, Healthcare Professional Checklist) related to the understanding of the important identified risks of SPRAVATO.	• Drug abuse • Transient dissociative states and perception disorders • Disturbances in consciousness • Blood pressure increased	Protocol submission (initial)	23 June 2020
			Start of data collection	Conduct of survey (wave 1): within 4 years of availability of the approved materials in selected countries. Conduct of survey (wave 2): within 4 to 5 years of availability of the approved materials in selected countries
			Final report	4Q 2024 A report on the educational activities undertaken and the results of the survey will be submitted within 4 years and no later than 5 years after launch. Updates are also reported in the PBRER/PSUR.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Drug abuse	**Routine risk communication:** • SmPC Section 4.4; • PL Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Administration under the direct supervision of an HCP (SmPC Sections 4.2 and 4.4, PL Section 3, and Instructions for Use). **Other routine risk minimization measures beyond the Product Information:** • Limited pack sizes; • Legal status: Special and restricted medical prescription with categorization at the Member State level.
Transient dissociative states and perception disorders	**Routine risk communication:** • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for dose adjustment are included in SmPC Section 4.2; • Recommendation for patients not to drive a motor vehicle or operate machinery until the next day after treatment following a restful sleep is included in SmPC Section 4.7 and PL Section 2; • Recommendation for postadministration observation is included in SmPC Section 4.2; • As described in SmPC Sections 4.2 and 4.4 and PL Section 3, administration and postadministration monitoring take place under the supervision of an HCP. **Other routine risk minimization measures beyond the Product Information:** • Legal status: Special and restricted medical prescription with categorization at the Member State level.

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Disturbances in consciousness	**Routine risk communication:** • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for dose adjustment are included in SmPC Section 4.2; • Recommendation for patients not to drive a motor vehicle or operate machinery until the next day after treatment following a restful sleep is included in SmPC Section 4.7 and PL Section 2; • Recommendation for postadministration observation is included in SmPC Section 4.2; • As described in SmPC Sections 4.2 and 4.4 and PL Section 2, administration and postadministration monitoring take place under the supervision an HCP. • Recommendation that administration and postadministration observation of SPRAVATO should be carried out in an appropriate clinical setting (SmPC Section 4.2). **Other routine risk minimization measures beyond the Product Information:** • Legal status: Special and restricted medical prescription with categorization at the Member State level.
Blood pressure increased	**Routine risk communication:** • SmPC Sections 4.2, 4.3, 4.4, and 4.8; • PL Sections 2 and 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding blood pressure assessment (before and after treatment), monitoring, and actions to manage blood pressure elevation are provided in SmPC Sections 4.2 and 4.4; • Recommendation regarding treatment in patients whose blood pressure is elevated prior to administration is provided in SmPC Section 4.4; • Recommendation not to administer SPRAVATO to patients in whom an elevation of blood pressure would present a serious risk is provided in SmPC Sections 4.2 and 4.3 and PL Section 2. • As described in SmPC Section 4.2, administration and postadministration monitoring take place under the supervision of HCPs with training in blood pressure monitoring. **Other routine risk minimization measures beyond the Product Information:** • Legal status: Special and restricted medical prescription with categorization at the Member State level.

V.2. Additional Risk Minimization Measures

Additional Risk Minimization 1	
Healthcare Professional Guide	
Objectives:	The Healthcare Professional Guide addresses the following important identified risks: • Drug abuse • Transient dissociative states and perception disorders • Disturbances in consciousness • Blood pressure increased The objectives of the Healthcare Professional Guide are to increase awareness of appropriate product administration (ie, under the direct supervision of an HCP), to increase awareness of the need for monitoring of blood pressure before and after dosing under the supervision of an HCP, and to educate HCPs about the following: • Whether a patient is eligible to use SPRAVATO. • The risk for abuse, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk. • Expected transient dissociative states/perception disorders and disturbances in consciousness and how to minimize potential adverse outcome from such effects. • Assessment, monitoring, and managing increased blood pressure, including hypertensive crisis. • Expected cardiovascular adverse effects. • The need for patient observation under the supervision of an HCP during and after dosing until the patient is stable based on clinical judgement. • The need for postdose monitoring by HCPs with training in blood pressure monitoring. • Only to initiate treatment with SPRAVATO in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. In these patients, SPRAVATO should be administered in a setting where appropriate resuscitation equipment and HCPs with training in cardiopulmonary resuscitation are available. • The influence of SPRAVATO on the patient's ability to drive or operate machinery and related instructions. • Minimum equipment for monitoring blood pressure.

Rationale for the additional risk minimization activity:	Ketamine is a drug of abuse, as it induces psychological effects including dissociation and other perceptual distortions; alterations in cognition; and changes in mood. Ketamine dependence has been reported in the literature. There is an attenuation of the dissociative effects. Evidence from an esketamine abuse potential study suggests that the potential for abuse is similar to that of ketamine. Transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure are expected effects of SPRAVATO based on esketamine's mechanism of action. Transient dissociative states and perception disorders, disturbances in consciousness, and transient increases in blood pressure have been observed in the clinical development program for esketamine nasal spray. The Healthcare Professional Guide helps HCPs to understand the key risks for SPRAVATO and is considered an essential additional measure to ensure proper, safe, and effective use of the product. Educating HCPs is important, especially considering that SPRAVATO requires specific measures before and after dosing.
Target audience and planned distribution path:	HCPs The national communication plan (including planned distribution) is agreed at the Member State level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Surveillance systems are used to detect signals based on reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the PBRER/PSUR. Assessments are conducted at the end of each PBRER/PSUR reporting interval. Stable reporting trends from postmarketing safety data are the criteria for success. A survey to assess the effectiveness of the Healthcare Professional Guide is ongoing.

Additional Risk Minimization 2

Patient Guide

Objectives:	The Patient Guide addresses the following important identified risks: • Drug abuse • Transient dissociative states and perception disorders • Disturbances in consciousness • Blood pressure increased The objectives of the Patient Guide are to: • Educate about what adverse effects to expect and how to minimize those effects. • Educate about the risk for abuse and dependence, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk. • Describe the drug administration procedure, including preparation (eg, fasting for 2 hours, no drinking for 30 minutes) and monitoring during the visit.

	• Increase awareness of: – Appropriate product administration (ie, under the direct supervision of an HCP). – The need for monitoring of blood pressure before and after dosing under the supervision of an HCP and the need for postdose observation until the HCP decides that the patient is stable based on clinical judgement. – The influence of SPRAVATO on the patient's ability to drive or operate machinery and related instructions.
Rationale for the additional risk minimization activity:	Ketamine is a drug of abuse, as it induces psychological effects including dissociation and other perceptual distortions; alterations in cognition; and changes in mood. Ketamine dependence has been reported in the literature. There is an attenuation of the dissociative effects. Evidence from an esketamine abuse potential study suggests that the potential for abuse is similar to that of ketamine. Transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure are expected effects of SPRAVATO based on esketamine's mechanism of action. Transient dissociative states and perception disorders, disturbances in consciousness, and transient increases in blood pressure have been observed in the clinical development program for esketamine nasal spray. The Patient Guide, which is provided to the patient by the HCP, helps patients to understand the key risks of SPRAVATO and is considered an essential additional measure to ensure proper, safe, and effective use of the product. Educating patients is important, especially considering that SPRAVATO requires specific measures before and after dosing.
Target audience and planned distribution path:	Patients The national communication plan (including planned distribution) is agreed at the Member State level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Surveillance systems are used to detect signals based on reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the PBRER/PSUR. Assessments are conducted at the end of each PBRER/PSUR reporting interval. Stable reporting trends from postmarketing safety data are the criteria for success. A survey to assess effectiveness of the Patient Guide is ongoing.

Additional Risk Minimization 3

Healthcare Professional Checklist

Objectives:	The Healthcare Professional Checklist addresses the following important identified risks: • Transient dissociative states and perception disorders • Disturbances in consciousness • Blood pressure increased The use of a checklist allows for an objective basis on which the HCP can determine when a patient is stable and may safely leave the postadministration monitoring setting.

Rationale for the additional risk minimization activity:	Transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure are expected effects of SPRAVATO based on esketamine's mechanism of action. Transient dissociative states and perception disorders, disturbances in consciousness, and transient increases in blood pressure have been observed in the clinical development program for esketamine nasal spray. The Healthcare Professional Checklist provides guidance to HCPs regarding supervision and assessment of patients during and after SPRAVATO administration, as well as management of an emergency. It is considered an essential additional measure to ensure proper, safe, and effective use of the product.
Target audience and planned distribution path:	HCPs The national communication plan (including planned distribution) is agreed at the Member State level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Surveillance systems are used to detect signals based on reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the PBRER/PSUR. Assessments are conducted at the end of each PBRER/PSUR reporting interval. Stable reporting trends from postmarketing safety data are the criteria for success. A survey to assess effectiveness of the Healthcare Professional Checklist is ongoing.

Additional Risk Minimization 4

Controlled Access Program

Objectives:	The Controlled Access Program addresses the important identified risk of Drug abuse. The objectives of the Controlled Access Program are to ensure that: • SPRAVATO is dispensed to the healthcare setting where administration takes place (as agreed at the Member State level based on local requirements and/or local healthcare systems). • SPRAVATO is administered in an appropriate setting. Requirements include blood pressure monitoring equipment and acknowledgement of receipt of additional educational materials (Healthcare Professional Guide, Patient Guide, Healthcare Professional Checklist). The details of the program are tailored to the Member State and agreed with the NCA prior to launch of the product.
Rationale for the additional risk minimization activity:	Ketamine is a drug of abuse, as it induces psychological effects including dissociation and other perceptual distortions; alterations in cognition; and changes in mood. Ketamine dependence has been reported in the literature. There is an attenuation of the dissociative effects. Evidence from an esketamine abuse potential study suggests that the potential for abuse is similar to that of ketamine.
Target audience and planned distribution path:	Not applicable

Plans to evaluate the effectiveness of the interventions and criteria for success:	There are no regulatory commitments to evaluate the effectiveness of the Controlled Access Program.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Drug abuse	**Routine risk minimization measures:** • SmPC Section 4.4; • PL Section 2. • Administration under the direct supervision of an HCP (SmPC Sections 4.2 and 4.4, PL Section 3, and Instructions for Use); • Limited pack sizes; • Legal status: Special and restricted medical prescription with categorization at the Member State level. **Additional risk minimization measures:** • Healthcare Professional Guide; • Patient Guide; • Controlled Access Program.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cumulative review of adverse events of interest including presentation and analysis of abuse-related serious adverse reactions in PBRER/PSUR. **Additional pharmacovigilance activities:** • Survey to assess the effectiveness of the additional risk minimization materials.

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Transient dissociative states and perception disorders	**Routine risk minimization measures:** • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4. • Recommendations for dose adjustment are included in SmPC Section 4.2; • Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2; • Recommendation for postadministration observation is included in SmPC Section 4.2; • As described in SmPC Sections 4.2 and 4.4 and PL Section 3, administration and postadministration monitoring take place under the supervision of an HCP. • Legal status: Special and restricted medical prescription with categorization at the Member State level. **Additional risk minimization measures:** • Healthcare Professional Guide; • Patient Guide; • Healthcare Professional Checklist.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cumulative review of adverse events of transient dissociative states and perception disorders at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR. **Additional pharmacovigilance activities:** • Survey to assess the effectiveness of the additional risk minimization materials.

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Disturbances in consciousness	**Routine risk minimization measures:** • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4. • Recommendations for dose adjustment are included in SmPC Section 4.2; • Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2; • Recommendation for postadministration observation is included in SmPC Section 4.2; • As described in SmPC Sections 4.2 and 4.4 and PL Section 2, administration and postadministration monitoring take place under the supervision of an HCP. • Recommendation that administration and postadministration observation of SPRAVATO should be carried out in an appropriate clinical setting (SmPC Section 4.2). • Legal status: Special and restricted medical prescription with categorization at the Member State level. **Additional risk minimization measures:** • Healthcare Professional Guide; • Patient Guide; • Healthcare Professional Checklist.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cumulative review of adverse events of disturbances in consciousness at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR. **Additional pharmacovigilance activities:** • Survey to assess the effectiveness of the additional risk minimization materials.

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Blood pressure increased	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4 and 4.8; • PL Sections 2 and 4. • Recommendations regarding blood pressure assessment (before and after treatment), monitoring, and actions to manage blood pressure elevation are provided in SmPC Sections 4.2 and 4.4; • Recommendation regarding treatment in patients whose blood pressure is elevated prior to administration is provided in SmPC Section 4.4; • Recommendation not to administer SPRAVATO to patients in whom an elevation of blood pressure would present a serious risk is provided in SmPC Sections 4.2 and 4.3 and PL Section 2. • As described in SmPC Section 4.2, administration and postadministration monitoring take place under the supervision of HCPs with training in blood pressure monitoring. • Legal status: Special and restricted medical prescription with categorization at the Member State level. **Additional risk minimization measures:** • Healthcare Professional Guide; • Patient Guide; • Healthcare Professional Checklist.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cumulative review of adverse events of blood pressure increased at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR. **Additional pharmacovigilance activities:** • Survey to assess the effectiveness of the additional risk minimization materials.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for SPRAVATO (Esketamine Nasal Spray)

This is a summary of the Risk Management Plan (RMP) for SPRAVATO (esketamine nasal spray). The RMP details important risks of SPRAVATO, how these risks can be minimized, and how more information will be obtained about SPRAVATO's risks and uncertainties (missing information).

SPRAVATO's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how SPRAVATO should be used.

This summary of the RMP for SPRAVATO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SPRAVATO's RMP.

I. The Medicine and What it is Used For

SPRAVATO is authorized for use as an antidepressant (AD) in adults with treatment-resistant major depressive disorder (TRD) or acute short-term treatment of psychiatric emergency due to major depressive disorder (see SmPC for the full indications). It contains an aqueous solution of esketamine hydrochloride as the active substance within a single-use nasal spray device that delivers two sprays, one spray to each nostril.

Further information about the evaluation of SPRAVATO's benefits can be found in SPRAVATO's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/spravato.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of SPRAVATO, together with measures to minimize such risks and the proposed studies for learning more about SPRAVATO's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of SPRAVATO, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of SPRAVATO is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of SPRAVATO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SPRAVATO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	Drug abuse Transient dissociative states and perception disorders Disturbances in consciousness Blood pressure increased
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Drug Abuse	
Evidence for linking the risk to the medicine	Evidence from an esketamine abuse potential trial (Trial 54135419TRD1015) suggests that the potential for abuse is similar to that of ketamine, a known drug of abuse recreationally. No evidence of drug-seeking behavior was observed, and no confirmed cases of diversion were reported in clinical trials of esketamine nasal spray.
Risk factors and risk groups	Risk factors and groups for substance abuse include mental health disorders (eg, depression, anxiety, and bipolar disorder), stressful environmental factors, taking addictive prescription medication, alcohol consumption, and family history of drug abuse and addiction. Dependence and attenuation to SPRAVATO may develop, particularly when not used as prescribed (eg, taking high doses on a daily basis over an extended period of time) or in individuals with a history of drug abuse or dependence.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4; • PL Section 2. • Administration under the direct supervision of an HCP (SmPC Sections 4.2 and 4.4, PL Section 3, and Instructions for Use); • Limited pack sizes; • Legal status: Special and restricted medical prescription with categorization at the Member State level. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Controlled Access Program.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Survey to assess effectiveness of the additional risk minimization materials. See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Transient Dissociative States and Perception Disorders	
Evidence for linking the risk to the medicine	Transient dissociative states and perception disorders are expected effects of SPRAVATO based on esketamine's mechanism of action, and have been observed in all phases of the clinical development program.
Risk factors and risk groups	Risk factors for transient dissociative states and perception disorders are unknown. There is a dose-response relationship between the esketamine dose and the severity of transient dissociative states/perception disorders, which is attenuated with repeated doses.

Important Identified Risk: Transient Dissociative States and Perception Disorders	
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4; • Recommendations for dose adjustment are included in SmPC Section 4.2; • Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2; • Recommendation for postadministration observation is included in SmPC Section 4.2; • As described in SmPC Sections 4.2 and 4.4 and PL Section 3, administration and postadministration monitoring take place under the supervision of an HCP. • Legal status: Special and restricted medical prescription with categorization at the Member State level. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Healthcare Professional Checklist.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Survey to assess effectiveness of the additional risk minimization materials. See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Disturbances in Consciousness	
Evidence for linking the risk to the medicine	Disturbances in consciousness such as sedation and somnolence are expected effects of SPRAVATO based on esketamine's mechanism of action, and have been observed in all phases of the clinical development program.
Risk factors and risk groups	Risk factors for sedation include old age (elderly patients) and use of concomitant sedatives.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4; • Recommendations for dose adjustment are included in SmPC Section 4.2; • Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2; • Recommendation for postadministration observation is included in SmPC Section 4.2; • As described in SmPC Sections 4.2 and 4.4 and PL Section 2, administration and postadministration monitoring take place under the supervision of an HCP. • Recommendation that administration and postadministration observation of SPRAVATO should be carried out in an appropriate clinical setting (SmPC Section 4.2). • Legal status: Special and restricted medical prescription with categorization at the Member State level. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Healthcare Professional Checklist.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Survey to assess effectiveness of the additional risk minimization materials. See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Blood Pressure Increased	
Evidence for linking the risk to the medicine	Cardiovascular effects due to increased blood pressure are expected for SPRAVATO based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the central nervous system that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure, as well as cardiovascular and blood pressure-related events, in association with esketamine nasal spray have been reported in the completed randomized, double-blind, controlled and open-label clinical trials. In clinical trials, elevations of blood pressure were transient, generally self-limiting, and did not require intervention.
Risk factors and risk groups	The risk of cardiovascular effects is greater in patients for whom an increase in blood pressure poses a serious risk, for example: • Patients who recently experienced a cardiovascular event, including myocardial infarction; • Patients with aneurysmal vascular disease (including intracranial, thoracic aorta, abdominal aorta, or peripheral arterial vessels); • Patients with history of intracerebral hemorrhage.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, and 4.8; • PL Sections 2 and 4. • Recommendations regarding blood pressure assessment (before and after treatment), monitoring, and actions to manage blood pressure elevation are provided in SmPC Sections 4.2 and 4.4; • Recommendation regarding treatment in patients whose blood pressure is elevated prior to administration is provided in SmPC Section 4.4; • Recommendation not to administer SPRAVATO to patients in whom an elevation of blood pressure would present a serious risk is provided in SmPC Sections 4.2 and 4.3 and PL Section 2. • As described in SmPC Section 4.2, administration and postadministration monitoring take place under the supervision of HCPs with training in blood pressure monitoring. • Legal status: Special and restricted medical prescription with categorization at the Member State level. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Healthcare Professional Checklist.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Survey to assess effectiveness of the additional risk minimization materials. See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of SPRAVATO.

II.C.2. Other Studies in Postauthorization Development Plan

PCSNSP002812: Survey to Assess the Effectiveness of SPRAVATO Educational Materials for Additional Risk Minimization Measures in the European Union

Purpose of the study: To assess the effectiveness of additional risk minimization materials (ie, Healthcare Professional Guide, Patient Guide, Healthcare Professional Checklist) related to the understanding of the important identified risks of Drug abuse, Transient dissociative states and perception disorders, Disturbances in consciousness, and Blood pressure increased.

A survey of HCPs involved in the prescription, administration, and management of SPRAVATO and of patients who use SPRAVATO is being conducted to measure the effectiveness of the educational materials to address the important identified risks associated with SPRAVATO treatment. Sampled HCPs involved in the prescription, administration and management of SPRAVATO treatment and patients who use SPRAVATO are asked to participate in the survey to assess knowledge and understanding of how to reduce important identified risks, in accordance with the educational materials.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Approved Key Messages of the Additional Risk Minimization Measures

Healthcare Professional Guide:

The Healthcare Professional Guide addresses the following important identified risks:

- Drug abuse
- Transient dissociative states and perception disorders
- Disturbances in consciousness
- Blood pressure increased

The objectives of the Healthcare Professional Guide are to increase awareness of appropriate product administration (ie, under the direct supervision of an HCP), to increase awareness of the need for monitoring of blood pressure before and after dosing under the supervision of an HCP, and to educate HCPs about the following:

- Whether a patient is eligible to use SPRAVATO.
- The risk for abuse, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk.
- Expected transient dissociative states/perception disorders and disturbances in consciousness and how to minimize potential adverse outcome from such effects.
- Assessment, monitoring, and managing increased blood pressure, including hypertensive crisis.
- Expected cardiovascular adverse effects.
- The need for patient observation under the supervision of an HCP during and after dosing until the patient is stable based on clinical judgement.
- The need for postdose monitoring by HCPs with training in blood pressure monitoring.
- Only to initiate treatment with SPRAVATO in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. In these patients, SPRAVATO should be administered in a setting where appropriate resuscitation equipment and HCPs with training in cardiopulmonary resuscitation are available.
- The influence of SPRAVATO on the patient's ability to drive or operate machinery and related instructions.
- Minimum equipment for monitoring blood pressure to be available at the site.

Healthcare Professional Guide: Sequence 0003/Module 1.8.2/HCPGuide.

Healthcare Professional Checklist:

The Healthcare Professional Checklist addresses the following important identified risks:

- Transient dissociative states and perception disorders
- Disturbances in consciousness
- Blood pressure increased

The objective of this checklist is to provide guidance to HCPs regarding supervision and assessment of patients during and after SPRAVATO administration, as well as management of an emergency.

Healthcare Professional Checklist: Sequence 0003/Module 1.8.2/Checklist.

Patient Guide:

The Patient Guide addresses the following important identified risks:

- Drug abuse
- Transient dissociative states and perception disorders
- Disturbances in consciousness
- Blood pressure increased

The objectives of the Patient Guide are to:

- Educate about what adverse effects to expect and how to minimize those effects.
- Educate about the risk for abuse and dependence, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk.
- Describe the drug administration procedure, including preparation (fasting for 2 hours, no drinking for 30 minutes) and monitoring during the visit.
- Increase awareness of:
  - Appropriate product administration (ie, under the direct supervision of an HCP).
  - The need for monitoring of blood pressure before and after dosing under the supervision of an HCP and the need for postdose observation until the HCP decides that the patient is stable based on clinical judgement.
  - The influence of SPRAVATO on the patient's ability to drive or operate machinery and related instructions.

Patient Guide: Sequence 0003/Module 1.8.2/PatientGuide.

Controlled Access Program

The Controlled Access Program addresses the important identified risk of Drug abuse. The objectives of the Controlled Access Program are to ensure that:

- SPRAVATO is dispensed to the healthcare setting where administration takes place (as agreed at the Member State level based on local requirements and/or local healthcare systems).
- SPRAVATO is administered in an appropriate setting. Requirements include blood pressure monitoring equipment and acknowledgement of receipt of additional educational materials.

The details of the program are tailored at national level with the NCA prior to launch of the product.