1. NAME OF THE MEDICINAL PRODUCT

SPRAVATO® (esketamine hydrochloride) 28mg nasal spray.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution.
Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SPRAVATO®, in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI), is indicated for adults with treatment-resistant Major Depressive Disorder (MDD), who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode (see section 5.1).

SPRAVATO® is indicated, in conjunction with an oral antidepressant, for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior.

Limitations of Use:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated (see section 5.1). Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.

- SPRAVATO® is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO® as an anesthetic agent have not been established.

4.2 Posology and method of administration

The decision to prescribe SPRAVATO® should be determined by a psychiatrist.

SPRAVATO® is intended to be self-administered by the patient under the direct supervision of a healthcare professional.

A treatment session consists of nasal administration of SPRAVATO® and a post-administration observation period. Both administration and post-administration observation of SPRAVATO® should be carried out in an appropriate clinical setting.

Assessment before treatment
Prior to dosing with SPRAVATO® blood pressure should be assessed.

If baseline blood pressure is elevated the risks of short-term increases in blood pressure and benefit of SPRAVATO® treatment should be considered (see section 4.4). SPRAVATO® should not be administered if an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.3).

Patients with clinically significant or unstable cardiovascular or respiratory conditions require additional precautions. In these patients, SPRAVATO® should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available (see section 4.4).

Post-administration observation
After dosing with SPRAVATO®, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted (see section 4.4).

Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting (see section 4.4).

Posology

Treatment-resistant Major Depressive Disorder
The dose recommendations for SPRAVATO® for treatment-resistant Major Depressive Disorder are shown in Table 1 and Table 2 (adults ≥65 years). 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 individualised to the lowest frequency to maintain remission/response.

Table 1: Recommended dosing for SPRAVATO® in adults <65 years with treatment-resistant Major Depressive Disorder

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 induction phase to determine need for continued treatment.	The need for continued treatment should be reexamined periodically.

Table 2: Recommended dosing for SPRAVATO® in adults ≥65 years with treatment-resistant Major Depressive Disorder	
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 induction phase to determine 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.

Depressive symptoms in patients with major depressive disorder with acute suicidal ideation or behaviour
Administer SPRAVATO® in conjunction with an oral antidepressant (AD).

The recommended dosage of SPRAVATO® for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. After 4 weeks of treatment with SPRAVATO®, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of SPRAVATO®, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior.

Food and liquid intake recommendations prior to administration
Since some patients may experience nausea and vomiting after administration of SPRAVATO®, patients should be advised not to eat for at least 2 hours before administration and not to drink liquids at least 30 minutes prior to administration (see section 4.8).

Nasal corticosteroid or nasal decongestant
Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medicinal products within 1 hour before SPRAVATO® administration.

Missed treatment session(s)

Patients who have missed treatment session(s) during the first 4 weeks of treatment should continue with their current dosing schedule.

For patients with treatment-resistant Major Depressive Disorder who miss treatment session(s) during maintenance phase and have worsening of depression symptoms, per clinical judgement, consider returning to the previous dosing schedule (see Tables 1 and 2).

Special populations

Elderly (65 years of age and older)

In elderly patients the initial SPRAVATO® dose for treatment-resistant Major Depressive Disorder is 28 mg esketamine (day 1, starting dose, see Table 2 above). Subsequent doses should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability.

SPRAVATO® has not been studied in elderly patients as acute short-term treatment of psychiatric emergency due to Major Depressive Disorder.

Hepatic impairment

No dose adjustment is necessary in patients with mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. However, the maximum dose of 84 mg should be used with caution in patients with moderate hepatic impairment.

SPRAVATO® has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is necessary in patients with mild to severe renal impairment. Patients on dialysis were not studied.

Paediatric population

The safety and efficacy of SPRAVATO® in paediatric patients aged 17 years and younger have not been established. There is no relevant use of SPRAVATO® in children less than 7 years of age.

Method of administration

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 two sprays (one spray per nostril). To prevent loss of medicinal product, the device should not be primed before use. It is intended for administration by the patient under the supervision of a healthcare professional, 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.

Sneezing after administration

If sneezing occurs immediately after administration, a replacement device should not be used.

Use of the same nostril for 2 consecutive sprays

If administration in the same nostril occurs, a replacement device should not be used.

Treatment discontinuation with SPRAVATO® does not require tapering off; based on data from clinical trials the risk of withdrawal symptoms is low.

4.3 Contraindications

- Hypersensitivity to the active substance, ketamine, or to any of the excipients listed in section 6.1
- Patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.8):
  - Patients with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
  - Patients with history of intracerebral haemorrhage.
  - Recent (within 6 weeks) cardiovascular event, including myocardial infarction (MI).

4.4 Special warnings and precautions for use

Neuropsychiatric and motor impairments

SPRAVATO® has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during the clinical trials (see section 4.8). These effects may impair attention, judgment, thinking, reaction speed and motor skills. At each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement (see section 4.7).

Respiratory depression

Respiratory depression may occur at high doses following rapid intravenous injection of esketamine or ketamine when used for anaesthesia. Rare cases of deep sedation have been reported. Concomitant use of SPRAVATO® with CNS depressants may increase the risk for sedation (see section 4.5). During post-marketing use, rare cases of respiratory depression have been observed. The majority of these cases have been reported with concomitant use of CNS depressants and/or in patients with comorbidities such as obesity, anxiety, cardiovascular and respiratory conditions. These events were transient in nature and resolved after verbal/tactile stimulation or supplemental oxygen. Close monitoring is required for sedation and respiratory depression.

Effect on blood pressure

SPRAVATO® can cause transient increases in systolic and/or diastolic blood pressure which peak at approximately 40 minutes after administration of the medicinal product and last approximately 1-2 hours (see section 4.8). A substantial increase in blood pressure could occur after any treatment session. SPRAVATO® is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.3). Before prescribing SPRAVATO®, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO® outweigh its risks.

In patients whose blood pressure prior to dose administration is judged to be elevated (as a general guide: >140/90 mmHg for patients <65 years of age and >150/90 mmHg for patients ≥65 years of age), it is appropriate to adjust lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with SPRAVATO®. If blood pressure is elevated prior to SPRAVATO® administration a decision to delay SPRAVATO® therapy should take into account the balance of benefit and risk in individual patients.

Blood pressure should be monitored after dose administration. Blood pressure should be measured around 40 minutes post-dose and subsequently as clinically warranted until values decline. If blood pressure remains elevated for a prolonged period of time, assistance should promptly be sought from practitioners experienced in blood pressure management. Patients who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

Patients with clinically significant or unstable cardiovascular or respiratory conditions

Only 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 healthcare professionals with training in cardiopulmonary resuscitation are available. Examples of conditions which should be considered include, but are not limited to:

- Significant pulmonary insufficiency, including COPD;
- Sleep apnoea with morbid obesity (BMI ≥35);
- Patients with uncontrolled brady- or tachyarrhythmias that lead to haemodynamic instability;
- Patients with a history of an MI. These patients should be clinically stable and cardiac symptom free prior to administration;
- Haemodynamically significant valvular heart disease or heart failure (NYHA Class III-IV).

Suicide/suicidal thoughts or clinical worsening

The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated (see section 5.1). Use of SPRAVATO® does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.

Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs, therefore, patients should be closely monitored. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Suicidality in children and adolescents

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- The indication(s) approved in paediatric for the particular drug should be clearly stated / included.

Drug abuse, dependence, withdrawal

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO®. Prior to prescribing SPRAVATO®, each patient's risk for abuse or misuse should be assessed and patients receiving esketamine should be monitored for the development of behaviours or conditions of abuse or misuse, including drug seeking behaviour, while on therapy.

Dependence and tolerance have been reported with prolonged use of ketamine. In individuals who were dependent on ketamine, withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations have been reported upon discontinuing ketamine.

Ketamine, the racemic mixture of arketamine and esketamine, is a medicinal product that has been reported to be abused. The potential for abuse, misuse and diversion of SPRAVATO® is minimised due to the administration taking place under the direct supervision of a healthcare professional. SPRAVATO® contains esketamine and may be subject to abuse and diversion.

Other populations at risk

SPRAVATO® should be used with caution in patients with the following conditions. These patients should be carefully assessed before prescribing SPRAVATO® and treatment initiated only if the benefit outweighs the risk:

- Presence or history of psychosis;
- Presence or history of mania or bipolar disorder;
- Hyperthyroidism that has not been sufficiently treated;
- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

Elderly (65 years of age and older)

Elderly patients treated with SPRAVATO® may have a greater risk of falling once mobilised, therefore, these patients should be carefully monitored.

Severe hepatic impairment

Due to expected increase in exposure and lack of clinical experience, SPRAVATO® is not recommended in patients with Child-Pugh class C (severe) hepatic impairment.

Hepatotoxicity has been reported with chronic ketamine use, therefore, the potential for such an effect due to long-term use of SPRAVATO® cannot be excluded. In a long-term clinical trial with patients treated for a mean total duration of exposure of 42.9 months (up to 79 months), no evidence of hepatotoxicity was observed.

Urinary tract symptoms

Urinary tract and bladder symptoms have been reported with SPRAVATO® use (see section 4.8). It is recommended to monitor for urinary tract and bladder symptoms during the course of treatment and refer to an appropriate healthcare provider when symptoms persist.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of SPRAVATO® with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation, which therefore should be closely monitored.

Blood pressure should be closely monitored when SPRAVATO® is used concomitantly with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) or other medicinal products that may increase blood pressure (e.g. xanthine derivatives, ergometrine, thyroid hormones, vasopressin, or MAOIs, such as, tranylcypromine, selegiline, phenelzine).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

SPRAVATO® is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pregnancy

There are no or limited data on the use of esketamine in pregnant women. Animal studies have shown that ketamine, the racemic mixture of arketamine and esketamine, induces neurotoxicity in developing foetuses (see section 5.3). A similar risk with esketamine cannot be excluded.

If a woman becomes pregnant while being treated with SPRAVATO®, treatment should be discontinued, and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible.

Breast-feeding

It is unknown whether esketamine is excreted in human milk. Data in animals have shown excretion of esketamine in milk. A risk to the suckling child cannot be excluded. 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.

Fertility

Animal studies showed that fertility and reproductive capacities were not adversely affected by esketamine.

4.7 Effects on ability to drive and use machines

SPRAVATO® has a major influence on the ability to drive and use machines. In clinical studies, SPRAVATO® has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety (see section 4.8). Before SPRAVATO® administration, patients should be instructed not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, until the next day following a restful sleep (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most commonly observed adverse reactions in patients treated with SPRAVATO® were dizziness (31%), dissociation (27%), nausea (27%), headache (23%), somnolence (18%), dysgeusia (18%), vertigo (16%), hypoaesthesia (11%), vomiting (11%), and blood pressure increased (10%).

Tabulated list of adverse reactions

Adverse reactions reported with esketamine are listed in the table below. Within the designated system organ classes, adverse reactions are listed under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Adverse Drug Reaction**			
	Frequency			
	Very common	**Common**	**Uncommon**	**Rare**

Psychiatric disorders	dissociation	anxiety, euphoric mood, confusional state, derealisation, irritability, hallucination including visual hallucination, agitation, illusion, panic attack, time perception altered	psychomotor retardation, emotional distress, dysphoria	
Nervous system disorders	dizziness, headache, somnolence, dysgeusia, hypoaesthesia	paraesthesia, sedation, tremor, mental impairment, lethargy, dysarthria, disturbance in attention	nystagmus, psychomotor hyperactivity	seizure
Eye disorders		vision blurred		
Ear and labyrinth disorders	vertigo	tinnitus, hyperacusis		
Cardiac disorders		tachycardia	bradycardia	
Vascular disorders		hypertension	hypotension	
Respiratory, thoracic and mediastinal disorders		nasal discomfort, throat irritation, oropharyngeal pain, nasal dryness including nasal crusting, nasal pruritus		respiratory depression
Gastrointestinal disorders	nausea, vomiting	hypoaesthesia oral, dry mouth	salivary hypersecretion	
Skin and subcutaneous tissue disorders		hyperhidrosis	cold sweat	
Renal and urinary disorders		pollakiuria, dysuria, micturition urgency		
General disorders and administration site conditions		feeling abnormal, feeling drunk, asthenia, crying, feeling of body temperature change	gait disturbance	
Investigations	blood pressure increased			

Long-term safety

Long-term safety was assessed in a Phase 3, multicentre, open-label extension study (TRD3008) in 1 148 adult patients with treatment-resistant Major Depressive Disorder representing 3 777

patient years of exposure. Patients were treated with esketamine for a mean total duration of exposure of 42.9 months (up to 79 months) with 63% and 28% of patients receiving treatment at least 3 years and 5 years, respectively. The safety profile of esketamine was consistent with the known safety profile observed in the pivotal clinical trials. No new safety concerns were identified.

Description of selected adverse reactions

Dissociation
Dissociation (27%) was one of the most common psychological effects of esketamine. Other related terms included derealisation (2.2%), depersonalisation (2.2%), illusions (1.3%), and distortion of time (1.2%). These adverse reactions were reported as transient and self-limited and occurred on the day of dosing. Dissociation was reported as severe in intensity at the incidence of less than 4% across studies. Dissociation symptoms typically resolved by 1.5 hours post-dose and the severity tended to reduce over time with repeated treatments.

Sedation/somnolence/respiratory depression
In clinical trials, adverse reactions of sedation (9.3%) and somnolence (18.2%) were primarily mild or moderate in severity, occurred on the day of dosing and resolved spontaneously the same day. Sedative effects typically resolved by 1.5 hours post-dose. Rates of somnolence were relatively stable over time during long-term treatment. In the cases of sedation, no symptoms of respiratory distress were observed, and haemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges. During post-marketing use, rare cases of respiratory depression have been observed (see section 4.4).

Changes in blood pressure
In clinical trials for treatment-resistant Major Depressive Disorder, increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO® plus oral antidepressants (see section 4.4). The frequency of markedly abnormal blood pressure elevations of SBP (≥40 mmHg increase) ranged from 8% (<65 years) to 17% (≥65 years) and DBP (≥25 mmHg increase) ranged from 13% (<65 years) to 14% (≥65 years) in patients receiving esketamine plus oral antidepressant. The incidence of increased SBP (≥ 180 mmHg) was 3% and DBP (≥ 110 mmHg) was 4%.

Cognitive and memory impairment
Cognitive and memory impairment have been reported with long-term ketamine use or drug abuse. These effects did not increase over time and were reversible after discontinuing ketamine. In long-term clinical trials, including a clinical trial with patients treated for a mean total duration of exposure of 42.9 months (up to 79 months), the effect of esketamine nasal spray on cognitive functioning was evaluated over time and performance remained stable.

Urinary tract symptoms
Cases of interstitial cystitis have been reported with daily and long-term ketamine use at high doses. In clinical studies with esketamine, there were no cases of interstitial cystitis, however a higher rate of lower urinary tract symptoms was observed (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine-treated patients compared with placebo-treated

patients. In a long-term clinical trial with patients treated for a mean total duration of exposure of 42.9 months (up to 79 months), no cases of interstitial cystitis were observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Depressive symptoms in patients with major depressive disorder with acute suicidal ideation or behavior

SPRAVATO® was evaluated for safety in 262 adults for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior (see section 5.1) from two Phase 3 studies (Study 3 and Study 4) and one Phase 2 study. Of all SPRAVATO®-treated patients in the completed Phase 3 studies, 184 (81%) received all eight doses over a 4-week treatment period.

Adverse reactions leading to discontinuation of treatment
In short-term studies in adults (pooled Study 3 and Study 4), the proportion of patients who discontinued treatment because of an adverse reaction was 6.2% for patients who received SPRAVATO® plus oral AD compared to 3.6% for patients who received placebo nasal spray plus oral AD. Adverse reactions leading to SPRAVATO® discontinuation in more than 1 patient were (in order of frequency): dissociation-related events (2.6%), blood pressure increased (0.9%), dizziness-related events (0.9%), nausea (0.9%), and sedation-related events (0.9%).

Most common adverse reactions
The most commonly observed adverse reactions in patients treated with SPRAVATO® plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo. Table 3 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO® plus oral AD and greater than patients treated with placebo nasal spray plus oral AD.

Table 3: Adverse Reactions Occurring in ≥2% of Adult Patients with MDD and Acute Suicidal Ideation or Behavior Treated with SPRAVATO® + Oral AD and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

	SPRAVATO® + Oral AD (N=227)	**Placebo + Oral AD (N=225)**
Cardiac disorders		
Tachycardia*	8 (4%)	2 (1%)
Ear and labyrinth disorders		
Vertigo	14 (6%)	1 (0.4%)
Gastrointestinal disorders		
Nausea	61 (27%)	31 (14%)

Vomiting	26 (11%)	12 (5%)
Constipation	22 (10%)	14 (6%)
Dry mouth	8 (4%)	6 (3%)
Toothache	5 (2%)	2 (1%)
General disorders and administration site conditions		
Feeling drunk	8 (4%)	1 (0.4%)
Feeling of relaxation	5 (2%)	3 (1%)
Investigations		
Blood pressure increased*	34 (15%)	14 (6%)
Musculoskeletal and connective tissue disorders		
Myalgia	5 (2%)	1 (0.4%)
Nervous system disorders		
Dizziness*	103 (45%)	34 (15%)
Sedation*	66 (29%)	27 (12%)
Dysgeusia*	46 (20%)	29 (13%)
Hypoesthesia*	30 (13%)	4 (2%)
Lethargy*	10 (4%)	4 (2%)
Confusional state	5 (2%)	0 (0%)
Psychiatric disorders		
Dissociation*	108 (48%)	30 (13%)
Anxiety*	34 (15%)	20 (9%)
Euphoric mood	17 (7%)	1 (0.4%)
Intentional self-injury	7 (3%)	3 (1%)
Dysphoria	5 (2%)	0 (0%)
Renal and urinary disorders		
Pollakiuria*	5 (2%)	2 (1%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	10 (4%)	3 (1%)
Throat irritation	9 (4%)	5 (2%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis*	11 (5%)	5 (2%)

* The following terms were combined:

Anxiety includes: agitation; anxiety; anxiety disorder; fear; irritability; nervousness; panic attack; psychomotor hyperactivity; tension

Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension

Dissociation includes: depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; hallucination; hallucination, auditory; hallucination, visual; hallucinations, mixed; hyperacusis; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnitus; vision blurred

Dizziness includes: dizziness; dizziness exertional; dizziness postural

Dysgeusia includes: dysgeusia; hypogeusia

Hyperhidrosis includes: cold sweat; hyperhidrosis

Hypoesthesia includes: hypoesthesia; hypoesthesia oral; intranasal hypoesthesia; pharyngeal hypoesthesia

Lethargy includes: fatigue; lethargy; psychomotor retardation

Pollakiuria includes: micturition urgency; pollakiuria

Sedation includes: sedation; somnolence; stupor

Tachycardia includes: heart rate increased; sinus tachycardia; tachycardia

Sedation

Sedation was evaluated by adverse event reports and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). In the MOAA/S, 5 means "responds readily to name spoken in normal tone" and 0 means "no response after painful trapezius squeeze." Any decrease in MOAA/S from pre-dose is considered to indicate the presence of sedation, and such a decrease occurred in a higher number of patients on SPRAVATO® than placebo during the short-term TRD studies. Dose-related increases in the incidence of sedation (MOAA/S score <5) were observed in a fixed-dose TRD study [see Warnings and Precautions (5.1)]. Table 4 presents the incidence of sedation (MOAA/S score <5) in a fixed-dose study with adult patients <65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

Table 4: Incidence of Sedation (MOAA/S Score <5) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients <65 Years of Age with TRD and Flexible-Dose Study with Patients ≥65 Years of Age with TRD)

	Patients <65 years			**Patients ≥65 years**	
	Placebo + Oral AD	**SPRAVATO® + Oral AD**		**Placebo + Oral AD**	**SPRAVATO® + Oral AD**
		56 mg	**84 mg**		**28 to 84 mg**
Number of patients*	**N=112**	**N=114**	**N=114**	**N=63**	**N=72**
Sedation (MOAA/S score <5)	11%	50%	61%	19%	49%

* Patients who were evaluated with MOAA/S

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, there was a higher incidence of sedation (MOAA/S score <5) in patients treated with SPRAVATO® plus oral AD compared to patients treated with placebo plus oral AD, similar to the TRD study results in Table 4.

Dissociation/perceptual changes

SPRAVATO® can cause dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the Clinician-Administered Dissociative States Scale (CADSS). A CADSS total score of more than 4 indicates the presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on SPRAVATO® compared to placebo during the short-term TRD studies. Dose-related increases in the incidence of dissociative symptoms (CADSS total score >4 and change >0) were observed in a fixed-dose TRD study [see Warnings and Precautions (5.2)]. Table 5 presents the incidence of dissociation (CADSS total score >4 and change >0) in a fixed-dose study with adult patients <65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

Table 5: Incidence of Dissociation (CADSS Total Score >4 and Change >0) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients <65 Years of Age with TRD and Flexible-Dose Study with Patients ≥65 Years of Age with TRD)

	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO® + Oral AD		Placebo + Oral AD	SPRAVATO® + Oral AD 28 to 84 mg
		56 mg	84 mg		
Number of patients*	**N=113**	**N=113**	**N=116**	**N=65**	**N=72**
CADSS total score >4 and change >0	5%	61%	69%	12%	75%

* Number of patients who were evaluated with CADSS

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO® plus oral AD also demonstrated a higher number (84%) with dissociation (CADSS total score >4 and change >0) compared to patients treated with placebo plus oral AD (16%).

Increase in blood pressure

The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients with TRD receiving SPRAVATO® plus oral antidepressants [see Warnings and Precautions (5.6)]. Table 6 presents increases in blood pressure in short-term trials with patients <65 years of age and ≥65 years of age with TRD.

Table 6: Increases in Blood Pressure in Double-blind, Randomized, Placebo-Controlled, Short-Term Trials of SPRAVATO® + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD in Adult Patients

	Patients <65 years		Patients ≥65 years	
	SPRAVATO® + Oral AD N=346	Placebo + Oral AD	SPRAVATO® + Oral AD N=72	Placebo + Oral AD N=65

		N=222		
Systolic blood pressure				
≥180 mmHg	9 (3%)	---	2 (3%)	1 (2%)
≥40 mmHg increase	29 (8%)	1 (0.5%)	12 (17%)	1 (2%)
Diastolic blood pressure				
≥110 mmHg	13 (4%)	1 (0.5%)	---	---
≥25 mmHg increase	46 (13%)	6 (3%)	10 (14%)	2 (3%)

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO® plus oral antidepressants demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patient with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥40 mmHg increases in SBP, and similar rates of increases to DBP ≥110 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results in Table 6.

Nausea and vomiting

SPRAVATO® can cause nausea and vomiting. Most of these events occurred on the day of dosing and resolved the same day, with the median duration not exceeding 1 hour in most subjects across dosing sessions. Rates of reported nausea and vomiting decreased over time across dosing sessions from the first week of treatment in the short-term studies, as well as over time with long-term treatment. Table 7 presents the incidence and severity of nausea and vomiting in a short-term study with patients with TRD.

Table 7: Incidence and Severity of Nausea and Vomiting in a Double-blind, Randomized, Placebo-Controlled, Fixed-Dose Study in Adult Patients with TRD

Treatment (+ Oral AD)	**N**	**Nausea**		**Vomiting**	
		All	**Severe**	**All**	**Severe**
SPRAVATO® 56 mg	115	31 (27%)	0	7 (6%)	0
SPRAVATO® 84 mg	116	37 (32%)	4 (3%)	14 (12%)	3 (3%)
Placebo Nasal Spray	113	12 (11%)	0	2 (2%)	0

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients demonstrated similar incidence and severity of reported nausea and vomiting compared to the TRD study results described above.

Sense of smell

Sense of smell was assessed over time; no difference was observed between patients treated with SPRAVATO® plus oral AD and those treated with placebo nasal spray plus oral AD during the double-blind maintenance phase of Study 2 (see section 5.1).

4.9 Overdose

The potential for overdose of SPRAVATO® by the patient is minimised due to the product's design and the administration taking place under the supervision of a healthcare professional (see section 4.2).

Symptoms

The maximum single esketamine nasal spray dose tested in healthy volunteers was 112 mg which showed no evidence of toxicity and/or adverse clinical outcomes. However, compared to the recommended dose range, the 112-mg esketamine nasal spray dose was associated with higher rates of adverse reactions, including dizziness, hyperhidrosis, somnolence, hypoaesthesia, feeling abnormal, nausea and vomiting.

Life-threatening symptoms are expected based on experience with ketamine given at 25-fold the usual anaesthetic dose. Clinical symptoms are described as convulsions, cardiac arrhythmias, and respiratory arrest. Administration of a comparable supratherapeutic dose of esketamine by the intranasal route is unlikely to be feasible.

Management

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple medicinal products involvement should be considered. Management of SPRAVATO® overdose should consist of treating clinical symptoms and relevant monitoring. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; Other antidepressants, ATC code: N06AX27.

Mechanism of action

Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive, antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.

Pharmacodynamic effects

Abuse potential
In a study of abuse potential conducted in recreational polydrug users (n=41), single doses of esketamine nasal spray (84 mg and 112 mg) and the positive control drug intravenous ketamine (0.5 mg/kg infused over 40 minutes) produced significantly greater scores than placebo on subjective ratings of “drug liking” and on other measures of subjective drug effects.

Clinical efficacy and safety

The efficacy and safety of SPRAVATO® nasal spray was investigated in five Phase 3 clinical studies (TRD3001, TRD3002, TRD3003, TRD3004, and TRD3005) in adult patients (18 to 86 years) with treatment-resistant depression (TRD) who met DSM-5 criteria for major depressive disorder and were non-responders to at least two oral antidepressants (ADs) treatments, of adequate dosage and duration, in the current major depressive episode. 1,833 adult patients were enrolled, of which 1,601 patients were exposed to SPRAVATO®. Additionally, 202 patients were randomised (122 patients received SPRAVATO®) in Phase 2 study TRD2005 in Japan, 252 patients were randomised (126 patients received SPRAVATO®) in Phase 3 study TRD3006 primarily in China, and 676 patients were randomised (334 patients received SPRAVATO®) in Phase 3 study TRD3013.

The efficacy and safety of SPRAVATO® nasal spray was investigated in two Phase 3 clinical studies in adult patients (18 to 64 years) with moderate to severe MDD (MADRS total score >28) who had affirmative responses to Mini International Neuropsychiatric Interview (MINI) questions B3 ("Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [i.e., about killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?"). 456 adult patients were enrolled, of which 227 patients were exposed to SPRAVATO®.

Treatment-resistant depression – Short-term studies

SPRAVATO® was evaluated in three Phase 3 short-term (4-week) randomised, double-blind, active-controlled studies in patients with TRD. Studies TRANSFORM-1 (TRD3001) and TRANSFORM-2 (TRD3002) were conducted in adults (18 to < 65 years) and Study TRANSFORM-3 (TRD3005) was conducted in adults ≥ 65 years of age. Patients in TRD3001 and TRD3002 initiated treatment with SPRAVATO® 56 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray on day 1. SPRAVATO® dosages were then maintained on 56 mg or titrated to 84 mg or matching placebo nasal spray administered twice-weekly during a 4-week double-blind induction phase. SPRAVATO® doses of 56 mg or 84 mg were fixed in Study TRD3001 and flexible in Study TRD3002. In Study TRD3005, patients (≥ 65 years) initiated treatment with SPRAVATO® 28 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray (day 1). SPRAVATO® dosages were titrated to 56 mg or 84 mg or matching placebo nasal spray administered twice-weekly during a 4-week double-blind induction phase. In the flexible dose studies, TRD3002 and TRD3005, up titration of SPRAVATO® dose was based on clinical judgement and dose could be down titrated based on tolerability. A newly initiated open-label oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) was initiated on day 1 in all studies. The selection of the newly initiated oral AD was determined by the investigator based on the patient's prior treatment history. In all short-term studies, the primary efficacy endpoint was change in MADRS total score from baseline to day 28.

Baseline demographic and disease characteristics for patient in TRD3002, TRD3001, and TRD3005 are presented in Table 8.

Table 8: Baseline demographic characteristics for TRD3002, TRD3001, and TRD3005 (full analysis sets)			
	Study TRD3002 (N=223)	Study TRD3001 (N=342)	Study TRD3005 (N=137)
Age, years			
Median (Range)	47.0 (19; 64)	47.0 (18; 64)	69.0 (65; 86)
Sex, n (%)			
Male	85 (38.1%)	101 (29.5%)	52 (38.0%)
Female	138 (61.9%)	241 (70.5%)	85 (62.0%)
Race, n (%)			
White	208 (93.3%)	262 (76.6%)	130 (94.9%)
Black or African American	11 (4.9%)	19 (5.6%)	--
Prior oral antidepressants with nonresponse (i.e., failed antidepressants)			
Number of specific antidepressants, n (%)			
2	136 (61.0%)	167 (48.8%)	68 (49.6%)
3 or more	82 (36.8%)	167 (48.8%)	58 (42.3%)
Newly initiated oral antidepressant medication initiated at randomisation, n (%)			
SNRI	152 (68.2%)	196 (57.3%)	61 (44.5%)
SSRI	71 (31.8%)	146 (42.7%)	76 (55.5%)
Withdrawn from study (for any reason), n/N (%)	30/227 (13.2%)	31/346 (9.0%)	16/138 (11.6%)

In the flexible dose study TRD3002, at day 28, 67% of the patients randomised to SPRAVATO® were on 84 mg. In study TRD3002, esketamine plus a newly initiated oral AD demonstrated clinically meaningful and statistical superiority compared to a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 9), and symptom reduction was observed as early as 24 hours post-dose.

In study TRD3001, a clinically meaningful treatment effect in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed favouring SPRAVATO® plus newly initiated oral AD compared with a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 9). In Study TRD3001, the treatment effect for the SPRAVATO® 84 mg plus oral AD group compared with oral AD plus placebo was not statistically significant.

In study TRD3005, at day 28, 64% of the patients randomised to SPRAVATO® were on 84 mg, 25% on 56 mg, and 10% on 28 mg. In study TRD3005, a clinically meaningful but not statistically significant treatment effect in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed favouring SPRAVATO® plus newly initiated oral AD compared with a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 9). Subgroup analyses suggest limited efficacy in the population over 75 years old.

Table 9: Primary efficacy results for change in MADRS total score for 4-week clinical trials (ANCOVA BOCF*)

Study no.	Treatment group[§]	Number of patients	Mean baseline score (SD)	LS mean change from baseline to end of week 4 (SE)	LS mean difference (95% CI)†
TRD3001	SPRAVATO® 56 mg + oral AD	115	37.4 (4.8)	-18.9 (1.3)	-4.3 (-7.8, -0.8)[#]
	SPRAVATO® 84 mg + oral AD	114	37.8 (5.6)	-16.2 (1.3)	-1.2 (-4.7, 2.3)[#]
	Oral AD + placebo nasal spray	113	37.5 (6.2)	-14.7 (1.3)	
TRD3002	SPRAVATO® (56 mg or 84 mg) + oral AD	114	37.0 (5.7)	-17.7 (1.3)	-3.5 (-6.7, -0.3)‡
	Oral AD + placebo nasal spray	109	37.3 (5.7)	-14.3 (1.3)	
TRD3005 (≥ 65 years)	SPRAVATO® (28 mg, 56 mg or 84 mg) + oral AD	72	35.5 (5.9)	-10.1 (1.7)	-2.9 (-6.5, 0.6)[#]
	Oral AD + placebo nasal spray	65	34.8 (6.4)	-6.8 (1.7)	

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; AD = antidepressant

***** ANCOVA analysis using Baseline Observation Carried Forward, which means that for a patient who discontinues from treatment, it is assumed that the depression level returns to the baseline level (i.e. the depression level is the same as before start of treatment)

§ Nasally administered esketamine or placebo; oral AD = a newly initiated AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline)

† Difference (SPRAVATO® + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline

‡ Treatment group that was statistically significantly superior to Oral AD + placebo nasal spray

Median unbiased estimate (i.e., weighted combination of the LS means of the difference from Oral AD + placebo nasal spray), and 95% flexible confidence interval

Response and remission rates

Response was defined as ≥ 50% reduction in the MADRS total score from baseline of the induction phase. Based on the reduction in MADRS total score from baseline, the proportion of patients in Studies TRD3001, TRD3002 and TRD3005 who demonstrated response to SPRAVATO® plus oral AD treatment was greater than for oral AD plus placebo nasal spray throughout the 4-week double-blind induction phase (Table 10).

Remission was defined as a MADRS total score ≤ 12. In all three studies, a greater proportion of patients treated with SPRAVATO® plus oral AD were in remission at the end of the 4-week double-blind induction phase than for oral AD plus placebo nasal spray (Table 10).

Table 10: Response and remission rates in 4-week clinical trials based on BOCF* data							
		Number of patients (%)					
		Response rate†					**Remission rate‡**
Study No.	**Treatment group§**	**24 hours**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 4**
TRD3001	SPRAVATO® 56 mg + oral AD	20 (17.4%)	21 (18.3%)	29 (25.2%)	52 (45.2%)	61 (53.0%)	40 (34.8%)
	SPRAVATO® 84 mg + oral AD	17 (14.9%)#	16 (14.0%)	25 (21.9%)	33 (28.9%)	52 (45.6%)	38 (33.3%)
	Oral AD + placebo nasal spray	8 (7.1%)	5 (4.4%)	15 (13.3%)	25 (22.1%)	42 (37.2%)	33 (29.2%)
TRD3002	SPRAVATO® 56 mg or 84 mg + oral AD	18 (15.8%)	15 (13.2%)	29 (25.4%)	54 (47.4%)	70 (61.4%)	53 (46.5%)
	Oral AD + placebo nasal spray	11 (10.1%)	13 (11.9%)	23 (21.1%)	35 (32.1%)	52 (47.7%)	31 (28.4%)
TRD3005 (≥ 65 years)	SPRAVATO® 28 mg, 56 mg or 84 mg + oral AD	NA	4 (5.6%)	4 (5.6%)	9 (12.5%)	17 (23.6%)	11 (15.3%)
	Oral AD + placebo nasal spray	NA	3 (4.6%)	8 (12.3%)	8 (12.3%)	8 (12.3%)	4 (6.2%)

AD = antidepressant; NA = not available

* Baseline Observation Carried Forward, which means that for a patient who discontinues from treatment, it is assumed that the depression level returns to the baseline level (i.e. the depression level is the same as before start of treatment).

§ Nasally administered SPRAVATO® or placebo; oral AD = a newly initiated AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline)

† Response was defined as ≥ 50% reduction in the MADRS total score from baseline

‡ Remission was defined as MADRS total score ≤ 12

First dose was SPRAVATO® 56 mg + oral AD

Treatment-resistant depression – Long-term studies

Relapse-prevention study

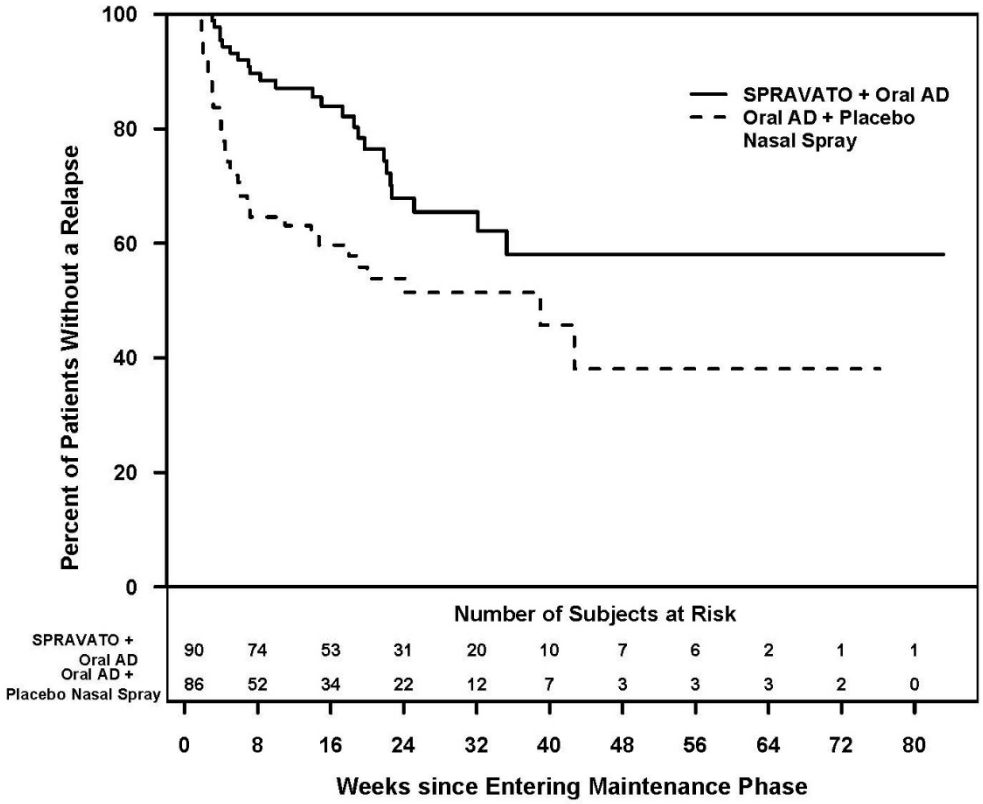
The maintenance of antidepressant efficacy was demonstrated in a relapse prevention trial. Study SUSTAIN-1 (TRD3003) was a long-term randomised, double-blind, parallel-group,

active-controlled, multicenter, relapse prevention study. The primary outcome measure to assess the prevention of depressive relapse was measured as time to relapse. Overall a total of 705 patients were enrolled; 437 directly enrolled; 150 transferred from TRD3001, and 118 transferred from TRD3002. Patients directly enrolled were administered SPRAVATO® (56 mg or 84 mg twice weekly) plus oral AD in a 4-week open label induction phase. At the end of the open label induction phase, 52% of patients were in remission (MADRS total score ≤ 12) and 66% of patients were responders (≥ 50% improvement in MADRS total score). Patients who were responders (455), continued receiving treatment with SPRAVATO® plus oral AD in a 12-week optimisation phase. After the induction phase, patients received SPRAVATO® weekly for 4 weeks and starting from week 8, an algorithm (based on the MADRS) was used to determine the dosing frequency; patients in remission (i.e., MADRS total score was ≤ 12) were dosed every other week, however, if the MADRS total score increased to > 12, then the frequency was increased to weekly dosing for the next 4 weeks; with the objective of maintaining the patient on the lowest dosing frequency to maintain response/remission. At the end of 16 weeks of treatment period, patients in stable remission (n=176) or stable response (n=121) were randomised to continue with SPRAVATO® or stop SPRAVATO® and switch to placebo nasal spray. Stable remission was defined as MADRS total score ≤ 12 in at least 3 of the last 4 weeks of the optimisation phase and stable response was defined as ≥ 50% reduction in the MADRS total score from baseline for the last 2 weeks of the optimisation phase, but not in stable remission.

Stable remission

Patients in stable remission who continued treatment with SPRAVATO® plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Figure 1). Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks or hospitalisation for worsening depression or any other clinically relevant event indicative of relapse. The median time to relapse for a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray group was 273 days, whereas the median was not estimable for SPRAVATO® plus oral AD, as this group never reached 50% relapse rate.

Figure 1: Time to relapse in patients in stable remission in study TRD3003 (full analysis set)

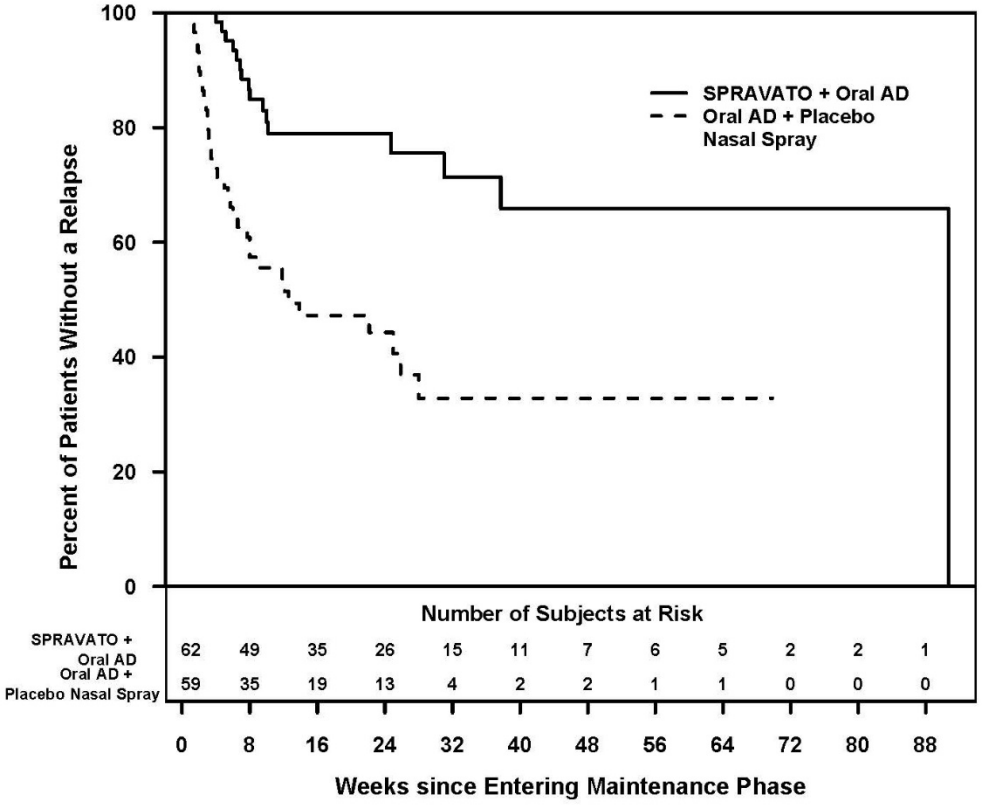


For patients in stable remission, the relapse rate based on Kaplan-Meier estimates during the 12- and 24-weeks double-blind follow up period was 13% and 32% for SPRAVATO® and 37% and 46% for placebo nasal spray, respectively.

Stable response

The efficacy results were also consistent for patients in stable response who continued treatment with SPRAVATO® plus oral AD; patients experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Figure 2). The median time to relapse for a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray group (88 days) was shorter compared to SPRAVATO® plus oral AD group (635 days).

Figure 2: Time to relapse in patients in stable response in study TRD3003 (full analysis set)



For patients in stable response, the relapse rate based on Kaplan-Meier estimates during the 12- and 24-weeks double-blind follow up period was 21% and 21% for SPRAVATO® and 47% and 56% for placebo nasal spray, respectively.

Enrollment in TRD3003 was staggered over approximately 2 years. The maintenance phase was of variable duration and continued until the individual patient had a relapse of depressive symptoms or discontinued for any other reason, or the study ended because the required number of relapse events occurred. Exposure numbers were influenced by the study stopping at a pre-determined number of relapses based on the interim analysis. After an initial 16 weeks of treatment with SPRAVATO® plus oral AD, the median duration of exposure to SPRAVATO® in the maintenance phase was 4.2 months (range: 1 day to 21.2 months) in SPRAVATO® -treated patients (stable remission and stable response). In this study, 31.6% of patients received SPRAVATO® for greater than 6 months and 7.9% of patients received SPRAVATO® for greater than 1 year in the maintenance phase.

Dosing frequency

The dosing frequency used the majority of the time during the maintenance phase is shown in Table 11. Of the patients randomised to SPRAVATO®, 60% received 84 mg and 40% received 56 mg dose.

Table 11: Dosing frequency used the majority of the time; maintenance phase (Study TRD3003)				
	Stable Remission		**Stable Responders**	
	SPRAVATO® + Oral AD (N=90)	**Oral AD + Placebo Nasal Spray (N=86)**	**SPRAVATO® + Oral AD (N=62)**	**Oral AD + Placebo Nasal Spray (N=59)**
Majority dosing frequency				
Weekly	21 (23.3%)	27 (31.4%)	34 (54.8%)	36 (61.0%)
Every other week	62 (68.9%)	48 (55.8%)	21 (33.9%)	19 (32.2%)
Weekly or every other week	7 (7.8%)	11 (12.8%)	7 (11.3%)	4 (6.8%)

Study TRD3013 (ESCAPE-TRD)

The efficacy of SPRAVATO® was evaluated in a long-term randomised, open-label, rater-blinded, active-controlled study (TRD3013) where SPRAVATO® was compared with quetiapine prolonged/extended-release (XR) in 676 adult patients (18-74 years) with TRD who continued to take their current oral AD (an SSRI or SNRI). Patients received treatment with flexibly dosed SPRAVATO® (28, 56, or 84 mg) or quetiapine XR, in line with the dosing recommendations in the SmPCs in use at the time of study initiation.

The primary efficacy endpoint was remission (MADRS total score of ≤ 10) at Week 8 and the key secondary endpoint was remaining relapse-free through Week 32 after remission at Week 8. Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks or hospitalisation for worsening depression or any other clinically relevant event indicative of relapse.

The baseline demographic and disease characteristics of patients were similar between the SPRAVATO® plus oral AD and quetiapine XR plus oral AD groups. The mean (SD) baseline MADRS total scores were 31.4 (6.06) for the SPRAVATO® plus oral AD group and 31.0 (5.83) for the quetiapine XR plus oral AD group.

SPRAVATO® plus oral AD demonstrated clinically meaningful and statistical superiority compared to quetiapine XR plus oral AD on both the primary (Table 12) and key secondary (Table 13) efficacy measure.

Table 12: Primary efficacy results for TRD3013 Study[a]

Treatment group	**SPRAVATO®+ oral AD**	**Quetiapine XR + oral AD**
Number of patients in remission at Week 8	91/336 (27.1%)	60/340 (17.6%)
Adjusted risk difference in percentage (95% CI) [b]	9.5 (3.3, 15.8)	–
P-value [c]	P = 0.003	–

CI = confidence interval; AD = antidepressant; XR = extended release

a A patient who discontinued study intervention before Week 8 was considered as a negative outcome (i.e. non remission). For patients for whom no MADRS result was available at the Week 8 visit but who did not discontinue study intervention or withdraw from study before Week 8, LOCF of MADRS was applied.
b Mantel-Haenszel estimate of the risk difference, stratified by age groups (18-64; ≥65) and total number of treatment failures is used. This estimated difference indicates an advantage for esketamine.
c Cochran–Mantel–Haenszel (CMH) test, adjusting for age groups (18-64; ≥65) and total number of treatment failures.

Table 13: Key secondary efficacy results for TRD3013 Study[a]

Treatment group	SPRAVATO® + oral AD	Quetiapine XR + oral AD
Number of patients both in remission at Week 8 and relapse-free at Week 32	73/336 (21.7%)	48/340 (14.1%)
Adjusted risk difference in percentage (95% CI) [b]	7.7 (2.0, 13.5)	–
P-value [c]	P = 0.008	–

CI = confidence interval; AD = antidepressant; XR = extended release
a A patient who discontinued study intervention was considered as a negative outcome. For patients for whom no MADRS result was available at the Week 8 visit but who did not discontinue study intervention or withdraw from study before Week 8, LOCF of MADRS was applied.
b Mantel-Haenszel estimate of the risk difference, stratified by age groups (18-64; ≥65) and total number of treatment failures is used. This estimated difference indicates an advantage for esketamine.
c Cochran–Mantel–Haenszel (CMH) test, adjusting for age groups (18-64; ≥65) and total number of treatment failures.

Treatment discontinuation rates over the 32-week treatment period due to adverse events, lack of efficacy, and overall were 4.2%, 8.3%, and 23.2% respectively for patients in the SPRAVATO® plus oral AD group and 11.5%, 15.0%, and 40.3% respectively for patients in the quetiapine XR plus oral AD group.

Treatment-resistant depression – Short-term study in Japanese patients

The efficacy of SPRAVATO® was also evaluated in a short-term (4-week) randomised, double-blind, active-controlled study (TRD2005) in 202 adult Japanese patients with TRD. Patients received 4 weeks of induction treatment with SPRAVATO® fixed-dose of 28 mg, 56 mg, 84 mg or placebo nasal spray in addition to continued current oral AD. The primary efficacy endpoint was change in MADRS total score from baseline to day 28. The baseline demographic and disease characteristics of patients were similar between the SPRAVATO® plus AD and placebo nasal spray plus AD groups.

In study TRD2005, no statistically significant difference in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed for any of the SPRAVATO® plus oral AD dosages compared with oral AD plus placebo nasal spray (Table 14).

Table 14: Primary efficacy results for change in MADRS total score for 4-week TRD2005 Study in Japanese patients (MMRM)

Treatment group	Number of patients	Mean baseline score (SD)	LS mean change from baseline to end of week 4 (SE)	LS mean difference (90% CI)[†,#]
SPRAVATO® 28 mg + oral AD	41	38.4 (6.1)	-15.6 (1.8)	-1.0 -5.77; 3.70
SPRAVATO® 56 mg + oral AD	40	37.9 (5.4)	-14.0 (1.9)	0.6 -4.32; 5.47
SPRAVATO® 84 mg + oral AD	41	35.9 (5.3)	-15.5 (1.8)	-0.9 -5.66; 3.83
Oral AD + placebo nasal spray	80	37.7 (5.7)	-14.6 (1.3)	

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; AD = antidepressant.

[†] Difference (SPRAVATO® + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline.

[#] Confidence interval is based on the Dunnett adjustment.

Treatment-resistant depression – Short-term study in Chinese patients

The efficacy of SPRAVATO® was also evaluated in a short-term (4-week) randomised, double-blind, active-controlled study (TRD3006) in 252 adult patients (224 Chinese patients, 28 non-Chinese patients) with TRD.

Patients received 4 weeks of induction treatment with flexibly dosed SPRAVATO® (56 mg or 84 mg) or placebo nasal spray, in addition to a newly initiated oral AD. The primary efficacy endpoint was change in MADRS total score from baseline to day 28. The baseline demographic and disease characteristics of patients were similar between the SPRAVATO® plus AD and placebo nasal spray plus AD groups.

In study TRD3006, no statistically significant difference in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed for SPRAVATO® plus oral AD compared with oral AD plus placebo nasal spray (Table 15).

Table 15: Primary efficacy results for change in MADRS total score for 4-week TRD3006 Study (MMRM)

Treatment group	Number of patients[#]	Mean baseline score (SD)	LS mean change from baseline to end of week 4 (SE)	LS mean difference (95% CI)[†]
All patients				
SPRAVATO® (56 mg or 84 mg) + oral AD	124	36.5 (5.21)	-11.7 (1.09)	-2.0 -4.64; 0.55
Oral AD + placebo nasal spray	126	35.9 (4.50)	-9.7 (1.09)	

Chinese population				
SPRAVATO® (56 mg or 84 mg) + oral AD	110	36.2 (5.02)	-8.8 (0.95)	-0.7 -3.35; 1.94
Oral AD + placebo nasal spray	112	35.9 (4.49)	-8.1 (0.95)	

SD = standard deviation; SE = standard error; LS Mean = least-squares mean;
CI = confidence interval; AD = antidepressant.

[#] Two patients did not receive oral AD and were not included in the efficacy analysis.

[†] Difference (SPRAVATO® + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline.

Depressive symptoms in patients with major depressive disorder with acute suicidal ideation or behavior

SPRAVATO® was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, Study 3 (NCT03039192) and Study 4 (NCT03097133), in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In these studies, patients received treatment with SPRAVATO® 84 mg or placebo nasal spray twice-weekly for 4 weeks. After the first dose, a one-time dose reduction to SPRAVATO® 56 mg was allowed for patients unable to tolerate the 84 mg dose. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (AD) (AD monotherapy or AD plus augmentation therapy) as determined by the investigator. After completion of the 4-week treatment period with SPRAVATO®/placebo, study follow-up continued through Day 90.

The baseline demographic and disease characteristics of patients in Study 3 and Study 4 were similar between the SPRAVATO® plus standard of care or placebo nasal spray plus standard of care treatment groups. The median patient age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of patients had at least one prior suicide attempt. Prior to entering the study, 92% of the patients were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of patients received AD monotherapy, 54% of patients received AD plus augmentation therapy, and 6% received both AD monotherapy/AD plus augmentation therapy.

The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In Study 3 and Study 4, SPRAVATO® plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care (see Table 16).

Table 16: Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies 3 and 4)

Study No.	Treatment Group[§]	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from	LS Mean Difference (95% CI)[†]

				Baseline to 24 hr Post First Dose (SE)	
Study 3	SPRAVATO® 84 mg + SOC‡	111	41.3 (5.87)	-15.9 (1.04)	-3.8 (-6.56; -1.09)
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.0 (1.02)	-
Study 4	SPRAVATO® 84 mg + SOC‡	113	39.4 (5.21)	-16.0 (1.02)	-3.9 (-6.60; -1.11)
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.2 (1.05)	-

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; SOC = standard of care.

§ SOC treatment included an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (antidepressant monotherapy or antidepressant monotherapy plus augmentation therapy).

† Difference (SPRAVATO® + SOC minus placebo nasal spray + SOC) in least-squares mean change from baseline.

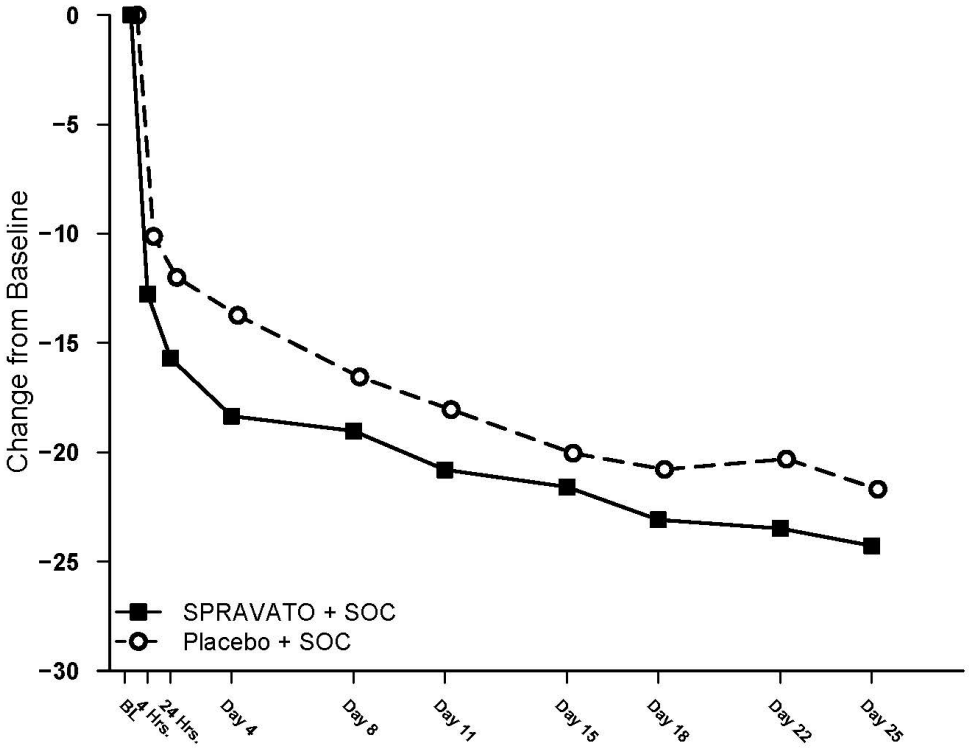
‡ SPRAVATO® + SOC were statistically significantly superior to placebo nasal spray + SOC.

The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after first dose (Day 2). The CGI-SS-r is a one-item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behavior. In Study 3 and Study 4, SPRAVATO® plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-r.

Time Course of Treatment Response

In both Study 3 and Study 4, SPRAVATO®'s treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, both the SPRAVATO® and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25. Figure 3 depicts time course of the primary efficacy measure of change in MADRS total score from Study 3.

Figure 3: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Study 3 (Full Analysis Set)



* Note: In Study 3, after the first dose, a one-time dose reduction to SPRAVATO® 56 mg was allowed for patients unable to tolerate the 84 mg dose. Approximately 19% of patients had reduction in SPRAVATO® dosage from 84 mg to 56 mg twice weekly.

5.2 Pharmacokinetic properties

Absorption

The mean absolute bioavailability of 84 mg esketamine administered as a nasal spray is approximately 48%.

Esketamine is rapidly absorbed by the nasal mucosa following nasal administration and can be measured in plasma within 7 minutes following a 28 mg dose. The time to reach maximum plasma concentration (t_{max}) is typically 20 to 40 minutes after the last nasal spray of a treatment session (see section 4.2).

Dose-dependent increases in the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{∞}) of esketamine nasal spray were produced by doses of 28 mg, 56 mg and 84 mg.

The pharmacokinetic profile of esketamine is similar after a single dose and repeat dose administration with no accumulation in plasma when esketamine is administered twice a week.

Distribution

The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.

The proportion of the total concentration of esketamine that is bound to proteins in human plasma is on average 43 to 45%. The degree to which esketamine is bound to plasma proteins is not dependent on hepatic or renal function.

Esketamine is not a substrate of transporters P-glycoprotein (P-gp; multidrug resistance protein 1), breast cancer resistance protein (BCRP), or organic anion transporter (OATP) 1B1, or OATP1B3. Esketamine does not inhibit these transporters or multi-drug and toxin extrusion 1 (MATE1) and MATE2-K, or organic cation transporter 2 (OCT2), OAT1, or OAT3.

Biotransformation

Esketamine is extensively metabolised in the liver. The primary metabolic pathway of esketamine in human liver microsomes is N-demethylation to form noresketamine. The main cytochrome P450 (CYP) enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A4. Other CYP enzymes, including CYP2C19 and CYP2C9, contribute to a much smaller extent. Noresketamine is subsequently metabolised via CYP-dependent pathways to other metabolites, some of which undergo glucuronidation.

Elimination

The mean clearance of esketamine administered by the intravenous route was approximately 89 L/hour. After C_{max} was reached following nasal administration, the decline in esketamine concentrations in plasma was rapid for the first few hours and then more gradual. The mean terminal half-life following administration as a nasal spray generally ranged from 7 to 12 hours.

Following intravenous administration of radiolabelled esketamine, approximately 78% and 2% of administered radioactivity was recovered in urine and faeces, respectively. Following oral administration of radiolabelled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and faeces, respectively. The recovered radioactivity consisted primarily of esketamine metabolites. For the intravenous and oral routes of administration, < 1% of the dose was excreted in the urine as unchanged drug.

Linearity/non-linearity

Esketamine exposure increases with dose from 28 mg to 84 mg. The increase in C_{max} and AUC values was less than dose-proportional between 28 mg and 56 mg or 84 mg, but it was nearly dose proportional between 56 mg and 84 mg.

Interactions

Effect of other medicinal products on esketamine

Hepatic enzyme inhibitors
Pre-treatment of healthy subjects with oral ticlopidine, an inhibitor of hepatic CYP2B6 activity, (250 mg twice daily for 9 days prior to and on the day of esketamine administration) had no effect on the C_{max} of esketamine administered as a nasal spray. The AUC_{∞} of esketamine was increased by approximately 29%. The terminal half-life of esketamine was not affected by ticlopidine pre-treatment.

Pre-treatment with oral clarithromycin, an inhibitor of hepatic CYP3A4 activity, (500 mg twice daily for 3 days prior to and on the day of esketamine administration) increase the mean C_{max} and AUC_{∞} of nasally administered esketamine by approximately 11% and 4%, respectively. The terminal half-life of esketamine was not affected by clarithromycin pre-treatment.

Hepatic enzyme inducers
Pre-treatment with oral rifampicin, a potent inducer of the activity of multiple hepatic CYP enzymes such as CYP3A4 and CYP2B6, (600 mg daily for 5 days prior to esketamine administration) decreased the mean C_{max} and AUC_{∞} values of esketamine administered as a nasal spray by approximately 17% and 28%, respectively.

Other nasal spray products
Pre-treatment of subjects with a history of allergic rhinitis and pre-exposed to grass pollen with oxymetazoline administered as a nasal spray (2 sprays of 0.05% solution administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.

Pre-treatment of healthy subjects with nasal administration of mometasone furoate (200 mcg per day for 2 weeks with the last mometasone furoate dose administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.

Effect of esketamine on other medicinal products

Nasal administration of 84 mg esketamine twice a week for 2 weeks reduced the mean plasma AUC_{∞} of oral midazolam (single 6 mg dose), a substrate of hepatic CYP3A4, by approximately 16%.

Nasal administration of 84 mg esketamine twice a week for 2 weeks did not affect the mean plasma AUC of oral bupropion (single 150 mg dose), a substrate of hepatic CYP2B6.

Special populations

Elderly (65 years of age and older)
The pharmacokinetics of esketamine administered as a nasal spray was compared between elderly but otherwise healthy subjects and younger healthy adults. The mean esketamine C_{max} and AUC_{∞} values produced by a 28-mg dose were 21% and 18% higher, respectively, in elderly subjects (age range 65 to 81 years) compared with younger adult subjects (age range 22 to 50 years). The mean esketamine C_{max} and AUC_{∞} values produced by an 84-mg dose were 67% and 38% higher in

elderly subjects (age range 75 to 85 years) compared with younger adult subjects (age range 24 to 54 years). The terminal half-life of esketamine was similar in the elderly and younger adult subjects (see section 4.2).

Renal impairment
Relative to the subjects with normal renal function (creatinine clearance [CL_{CR}], 88 to 140 mL/min), the C_{max} of esketamine was on average 20 to 26% higher in subjects with mild (CL_{CR}, 58 to 77 mL/min), moderate (CL_{CR}, 30 to 47 mL/min), or severe (CL_{CR}, 5 to 28 mL/min, not on dialysis) renal impairment following administration of a 28-mg dose of esketamine nasal spray. The AUC_{∞} was 13 to 36% higher in the subjects with mild to severe renal impairment.

There is no clinical experience with esketamine administered as a nasal spray in patients on dialysis.

Hepatic impairment
The C_{max} and AUC_{∞} of esketamine produced by a 28-mg doses were similar between subjects with Child-Pugh class A (mild) hepatic impairment and healthy subjects. The C_{max} and AUC_{∞} of esketamine were 8% higher and 103% higher, respectively, in subjects with Child-Pugh class B (moderate) hepatic impairment, relative to healthy subjects.

There is no clinical experience with esketamine administered as a nasal spray in patients with Child-Pugh class C (severe) hepatic impairment (see section 4.2 and 4.4).

Race
The pharmacokinetics of esketamine nasal spray was compared between healthy Asian subjects and Caucasian subjects. Mean plasma esketamine C_{max} and AUC_{∞} values produced by a single, 56-mg dose of esketamine were approximately 14% and 33% higher, respectively, in Chinese subjects compared to Caucasians. On average, esketamine C_{max} was 10% lower and AUC_{∞} was 17% higher in Korean subjects, relative to Caucasian subjects. A population pharmacokinetic analysis was conducted that included Japanese patients with treatment resistant depression, in addition to healthy Japanese subjects. Based on this analysis, for a given dose, the plasma esketamine C_{max} and AUC_{24h} in Japanese subjects were approximately 20% higher relative to non Asian subjects. The mean terminal half-life of esketamine in the plasma of Asian subjects ranged from 7.1 to 8.9 hours and was 6.8 hours in Caucasian subjects.

Gender and body weight
No significant differences in the pharmacokinetics of esketamine nasal spray were observed for gender and total body weight (> 39 to 170 kg) based on population PK analysis.

Allergic rhinitis
The pharmacokinetics of a single, 56-mg dose of esketamine administered as a nasal spray was similar in subjects with allergic rhinitis who were exposed to grass pollen compared to healthy subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, neurotoxicity, reproductive toxicity, and carcinogenic potential. Animal studies with ketamine showed evidence of developmental neurotoxicity. The potential for esketamine to have neurotoxic effects on developing foetuses cannot be excluded (see section 4.6).

Genotoxicity

Esketamine was not mutagenic with or without metabolic activation in the Ames test. Genotoxic effects with esketamine were seen in a screening *in vitro* micronucleus test in the presence of metabolic activation. However, intravenously-administered esketamine was devoid of genotoxic properties in an *in vivo* bone marrow micronucleus test in rats and an *in vivo* Comet assay in rat liver cells.

Reproductive toxicity

In an embryo foetal developmental toxicity study with nasally administered ketamine in rats, the offspring was not adversely affected in the presence of maternal toxicity at doses resulting in exposure up to 6-fold higher than human exposure, based on AUC values. In an embryo foetal developmental toxicity study with nasally administered ketamine in rabbits, skeletal malformations were observed and foetal body weight was reduced at maternally toxic doses. Exposure in rabbits was in the region of human exposure based on AUC values.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain, that can be associated with prolonged cognitive deficiencies. The clinical significance of these non-clinical findings in not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.
See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store above 30ºC.
Keep out of the sight and reach of children.

6.5 Nature and contents of container

Type-I glass vial with a chlorobutyl rubber stopper. The filled and stoppered vial is assembled into a manually-activated nasal spray device. The device dispenses two sprays.

Within each pack, each device is individually packaged in a sealed blister.

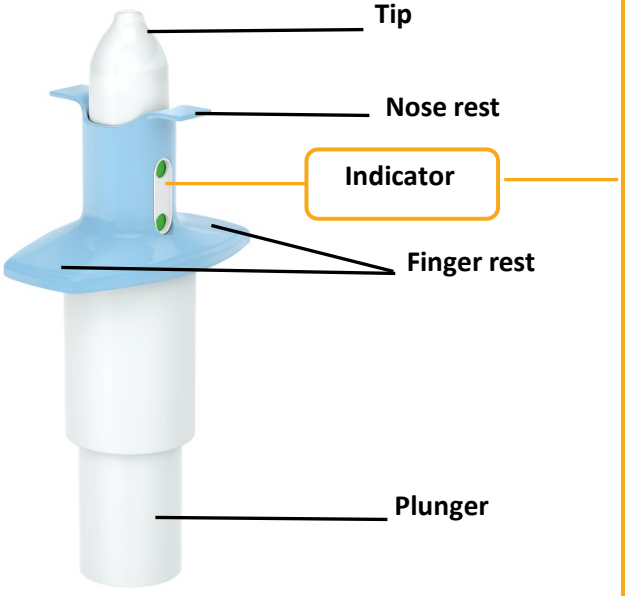
Pack sizes of 1, 2, 3, or 6 nasal spray devices.

Not all pack sizes may be marketed.

6.6 Special precautions for use and handling and disposal

This device is intended for administration by the patient, under supervision of a healthcare professional. Read this Instructions for Use in full before training and supervising patient.

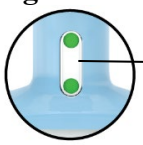
Nasal Spray Device



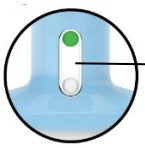
Indicator

One device contains 2 sprays.
(1 spray for each nostril)

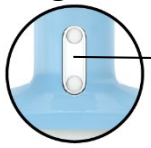
2 green dots (0 mg delivered)



1 green dot

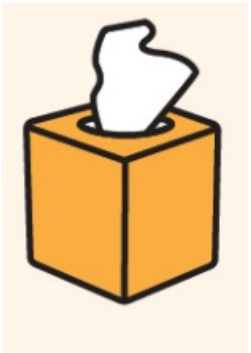


No green dots (28 mg delivered)

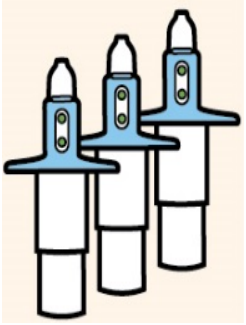


Step 1 Get ready

Before first device only:



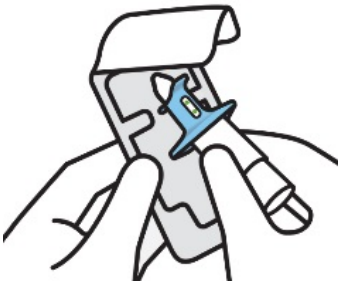
Instruct patient to blow nose **before first device only**.



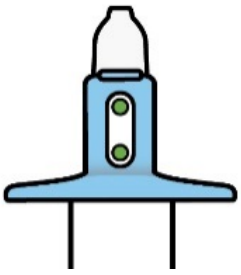
Confirm required number of devices.

28 mg = 1 device
56 mg = 2 devices
84 mg = 3 devices

Step 2 **Prepare device**



Healthcare professional: Check expiration date ('EXP'). If expired, get a new device. Peel blister and remove device.

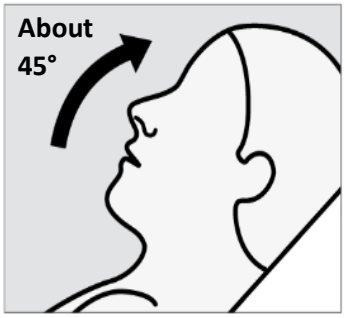


Healthcare professional: Do not prime device. This will result in a loss of medication. Check that indicator shows 2 green dots. If not, dispose of device and get a new one.

Hand device to patient.

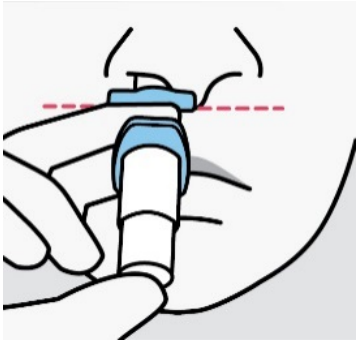
Step 3 Prepare patient

Patient should: Hold device as shown with the thumb gently supporting the plunger. Do not press the plunger.

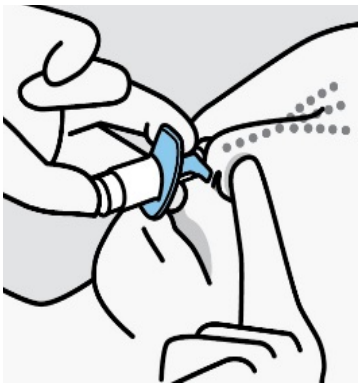


Patient should: Recline head at about 45 degrees during administration to keep medication inside the nose.

Step 4 Patient sprays once into each nostril

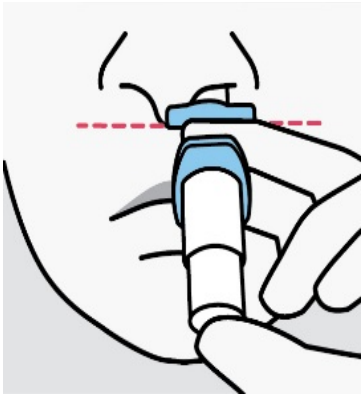


Patient should: Insert tip straight into the first nostril. Nose rest should touch the skin between the nostrils.



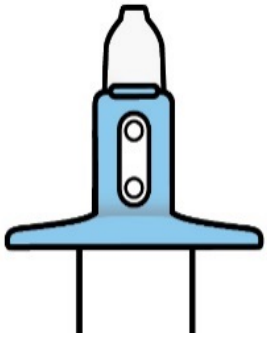
Patient should: Close opposite nostril. Breathe in through nose while pushing plunger all the way up until it stops.

Patient should: Sniff gently after spraying to keep medication inside nose.



Patient should: Switch hands to insert tip into the second nostril. Repeat Step 4 to deliver second spray.

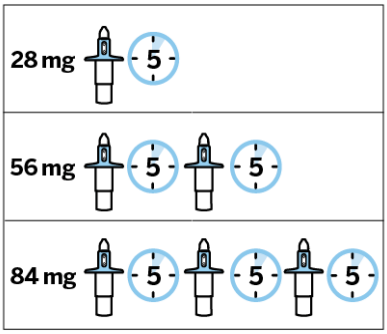
Step 5 Confirm delivery and rest



Healthcare professional: Take device from patient. Check that indicator shows **no green dots**. If you see a green dot, have patient spray again into the second nostril. Check indicator again to confirm device is empty.

Patient should: Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**. **Do not** blow nose. If liquid drips out, dab nose with a tissue.

Next device (if required)



Healthcare professional: Repeat Steps 2-5 if more than one device is required. Ensure that patient **waits 5 minutes after each device** to allow medication to absorb.

Dispose of used device(s) in accordance with local requirements.

7. MANUFACTURER

Renaissance Lakewood LLC
1200 Paco Way,
Lakewood, New Jersey (NJ),
08701, United States (USA).

8. PRODUCT REGISTRATION HOLDER

Johnson & Johnson Sdn Bhd (3718-D)
Level 8, The Pinnacle,
Persiaran Lagoon, Bandar Sunway,
46150, Petaling Jaya, Selangor, Malaysia

9. DATE OF REVISION OF THE TEXT

14 January 2024 (EU SmPC v12Dec2024 + US PI vJul2020)