SPRAVATO®

esketamine hydrochloride

DATA SHEET

1. PRODUCT NAME

SPRAVATO® esketamine hydrochloride 32.3mg (equivalent to 28mg esketamine) nasal spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single use nasal spray device delivers two sprays, one spray into each nostril. Total volume of drug product per device to be delivered is 0.2 mL containing a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine).

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Nasal spray, solution.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

SPRAVATO in conjunction with an oral antidepressant, is indicated for:

- treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode).
- rapid reduction of depressive symptoms in patients with Major Depressive Disorder who have acute suicidal ideation or behaviour.

SPRAVATO is not indicated to prevent suicide or in reducing suicidal ideation or behaviour (see section 4.4. Special Warnings And Precautions For Use)

4.2 Dose and method of administration

In patients with TRD, SPRAVATO should be administered in conjunction with a newly initiated oral antidepressant (AD) therapy.

In patients with MDSI, SPRAVATO should be administered in conjunction with standard of care therapy. During the Phase III MDSI clinical program, standard of care oral AD treatment (either AD monotherapy or AD plus augmentation therapy) was initiated or optimised.

Important Considerations Prior to Initiating and During Therapy

SPRAVATO must be administered under the direct supervision of a healthcare provider.
A treatment session consists of nasal administration of SPRAVATO and post-administration observation under supervision.

Blood Pressure Assessment Before and After Treatment

Assess blood pressure prior to dosing with SPRAVATO (see section 4.4 Special Warnings And Precautions For Use).

If baseline blood pressure is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of SPRAVATO treatment (see section 4.4 Special Warnings And Precautions For Use). Do not administer SPRAVATO if an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.3 Contraindications).

After dosing with SPRAVATO, reassess blood pressure at approximately 40 minutes and subsequently as clinically warranted.

If blood pressure is decreasing and the patient appears clinically stable, the patient may leave at the end of the post-dose monitoring period; if not, continue to monitor (see section 4.4 Special Warnings and Precautions For Use).

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 Undesirable Effects – Nausea and Vomiting).

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 medications within 1 hour before administration of SPRAVATO.

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 medication, 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.

For instructions to prepare the patient and for use of the nasal spray device, see also the Consumer Medicine Information and the “Instructions for Use” leaflet provided separately in the carton.

Dosage – Adults

Treatment-Resistant Depression

The dosage recommendations for SPRAVATO for TRD are shown in Table 1. Dose adjustments should be made based on efficacy and tolerability to the previous dose.

Table 1: Recommended Dosing for SPRAVATO for TRD

Induction Phase	**Maintenance Phase**
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	**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.	Periodically re-examine the need for continued treatment.

* For patients ≥65 years Day 1 starting dose is 28 mg

** Dosing frequency should be individualised to the lowest frequency to maintain remission/response.

After depressive symptoms improve, treatment should continue for at least 6 months.

Major Depressive Disorder with Acute Suicidal Ideation or Behaviour

The recommended dosage for SPRAVATO for patients with MDD who have acute suicidal ideation or behaviour 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 antidepressant (AD) therapy should be continued, per clinical judgement.

Patients who also have TRD should be evaluated to determine need for continued treatment with SPRAVATO beyond 4 weeks.

Post administration observation

During and after SPRAVATO administration at each treatment session, a healthcare professional should observe the patient until the patient is stable based on clinical judgment. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery until the next day after a restful sleep (see section 4.4 Special Warnings and Precautions for Use- Effect on blood pressure; Potential for cognitive and motor impairment; Effect on driving).

Missed treatment session(s)

If a patient misses treatment session(s) during the first 4 weeks of treatment, patients should continue their current dosing schedule.

For patients with TRD 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 Table 1).

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of SPRAVATO have not been established in patients aged 17 years and younger.

Elderly (65 years of age and older)

In elderly patients the initial SPRAVATO dose is 28 mg (Day 1, Starting Dose, see Table 1). Subsequent doses should be increased in increments of 28 mg, up to 56 mg or 84 mg, based on efficacy and tolerability.

Hepatic impairment

No dosage adjustment is necessary in patients with mild (Child Pugh class A) or moderate (Child Pugh class B) 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 section 5.2 Pharmacokinetic Properties).

Japanese and Chinese patients with treatment-resistant depression

Efficacy of SPRAVATO in Japanese and Chinese patients has not been established.

4.3 Contraindications

SPRAVATO is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.4 Special Warnings and Precautions for use):

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

SPRAVATO is contraindicated in patients with a known hypersensitivity to esketamine, ketamine, or to any of the excipients.

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated.

Use of SPRAVATO for the rapid reduction of depressive symptoms in adult patients with Major Depressive Disorder who have acute suicidal ideation or behaviour does not preclude the need for hospitalisation, if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO.

Closely monitor all antidepressant-treated patients including patients treated with SPRAVATO for clinical worsening or emergence of suicidal thoughts and behaviours, especially during the initial few months of drug therapy and at times of dosage changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior 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.

Effect on blood pressure

SPRAVATO can cause transient increases in systolic and/or diastolic blood pressure which peak at approximately 40 minutes after drug administration and last approximately 1-2 hours (see section 4.8 Undesirable Effects). Patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing SPRAVATO and treatment initiated only if the benefit outweighs the risk (see section 4.3 Contraindications). Examples of conditions which should be carefully considered include:

- Unstable or poorly controlled hypertension.
- History (within 6 weeks) of cardiovascular event, including myocardial infarction (MI). Patients with a history of an MI should be clinically stable and cardiac symptom free prior to dosage administration.
- History (within 6 months) of ischemic stroke or transient ischemic attack.
- Haemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
- New York Heart Association (NYHA) Class III IV heart failure of any aetiology.

Administration of SPRAVATO can temporarily raise blood pressure lasting approximately 1-2 hours. Blood pressure should be assessed prior to dosing with SPRAVATO. In patients whose blood pressures prior to dose administration are 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 consider lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with SPRAVATO. The decision whether or not 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 until blood pressure returns to acceptable levels. If blood pressure remains too high, 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.

Respiratory depression

During post-marketing use, rare cases of respiratory depression have been observed (see section 4.8 Undesirable Effects). The majority of these cases have been reported with the use of SPRAVATO in combination with other 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. Patients should be monitored for respiratory depression.

Potential for cognitive and motor impairment

SPRAVATO has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during the clinical trials (see section 4.8 Undesirable Effects). These effects may impair attention, judgment, thinking, reaction speed and motor skills. Tolerance to above effects may develop after a few treatment sessions. At each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered clinically stable (see section 4.2 Dose and Method of Administration).

Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment

Long-term 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 the clinical trials, including a long-term clinical trial with patients treated for a median duration of 45.8 months (up to 79 months), the effect of esketamine nasal spray on cognitive functioning was evaluated over time and performance remained stable.

Effect on driving

Two studies were conducted to assess the effects of SPRAVATO on the ability to drive (see section 5.1 Pharmacodynamic Properties – Pharmacodynamic effects: Effects on driving). Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor co-ordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep (see section 4.4 Special Warnings and Precautions for Use – Potential for Cognitive and Motor Impairment).

Bladder effects

Cases of interstitial cystitis have been reported in subjects using ketamine for recreational use or for treatment of chronic pain at high doses with long-term use. In clinical studies with esketamine nasal spray, subjects were assessed for symptoms of cystitis, bladder pain and interstitial cystitis. No cases of esketamine related interstitial cystitis were observed in any of the studies, which involved treatment for up to 79 months (see section 5.1 Pharmacodynamic Properties – Clinical Trials).

Drug abuse and dependence

Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Careful consideration is advised prior to treatment of individuals with a history of substance use disorder, including alcohol. Monitoring for signs of abuse or dependence is recommended.

The potential for abuse, misuse and diversion of SPRAVATO is minimised due to the product's design and the administration taking place under the supervision by a healthcare professional.

Ketamine, the racemic mixture of arketamine and esketamine, has been reported as a drug of abuse. 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.

Dependence

Dependence and tolerance have been reported with prolonged use of ketamine. Individuals who were dependent on ketamine reported withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations. Monitoring for signs of dependence is recommended.

Hepatotoxicity

Hepatotoxicity has been reported with chronic ketamine use, ketamine is a racemic mixture containing esketamine therefore, the potential for such an effect due to long term use of SPRAVATO cannot be excluded.

Use in the elderly

Of the total number (N=1601) of patients in Phase 3 clinical studies exposed to SPRAVATO, n=194 (12.1%) were 65 years of age and older, while n=25 (1.6%) were 75 years of age and older. No overall differences in the safety profile were observed between these patients and patients younger than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic analysis showed that mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients (see section 5.2 Pharmacokinetic Properties – special populations, Elderly). Therefore, the recommended initial dose of SPRAVATO in elderly patients is lower than that for younger adults (see section 4.2 Dose and Method of Administration – Special populations, Elderly).

Evidence of efficacy has been observed in patients 65 and older (see section 5.1 Pharmacodynamic Properties – Clinical Trials).

Paediatric use

The safety and efficacy of SPRAVATO have not been established in patients aged 17 years and younger.

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
- Significant pulmonary insufficiency
- Patients with known uncontrolled bradyarrhythmias or tachyarrhythmias that lead to haemodynamic instability
- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

Effects of laboratory tests

SPRAVATO has not been associated with any clinically important changes to laboratory parameters in serum chemistry, haematology, or urinalysis.

4.5 Interactions with other medicines and other forms of interactions

Pharmacodynamic interactions

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

Concomitant use with monoamine oxidase inhibitors (MAOIs) (e.g., tranylcypromine, selegiline, phenelzine) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

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 (see section 5.2 Pharmacokinetic Properties).

Effect of other drugs 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 maximum plasma concentration (C_{max}) of esketamine administered as a nasal spray. The area under the plasma concentration time curve (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

Concomitant use of SPRAVATO with other nasally administered medicinal products has been evaluated in the following pharmacokinetic interaction studies. Pre-treatment of subjects with 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. (see section 4.2 Dose and Method of Administration- Method of administration)

Effect of esketamine on other drugs

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.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy- Category B3

SPRAVATO should not be used during pregnancy. The risks of SPRAVATO during pregnancy have not been studied. Human data in pregnant women during clinical trials with esketamine exposure are too limited to be conclusive. Animal studies with ketamine, the racemic mixture of arketamine and esketamine, show evidence of developmental neurotoxicity (see below). The potential for esketamine to have neurotoxic effects on foetuses cannot be excluded. To avoid exposing the foetus to esketamine, women of reproductive potential should be advised to use highly effective contraception during and up to 6 weeks after the last treatment with SPRAVATO. If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible.

Ketamine, the racemic mixture of arketamine and esketamine, administered intravenously at high anaesthetic dose levels to female rats in the second trimester of pregnancy caused neuronal cell abnormalities in the brains of their offspring which showed behavioural changes and impaired memory up to young adult age. When female monkeys were treated intravenously with ketamine at high anaesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their foetuses. Ketamine induced neuronal cell death was also observed with early

postnatal intraperitoneal or subcutaneous treatment of rat and mice pups, a period of rapid brain growth. This period of brain development translates into the third trimester of human pregnancy. In embryo foetal developmental toxicity studies in rats nasally administered ketamine did not induce adverse findings in the offspring. Skeletal malformations were found in the offspring of rabbits nasally treated with ketamine. It cannot be excluded that esketamine induces neurotoxicity in developing foetuses (see section 5.3 Preclinical Safety Data- Reproductive Toxicity).

Breast feeding

SPRAVATO should not be used in women who are breast feeding. The risks of SPRAVATO during breast feeding have not been studied in humans. There are no data available to assess the effects of esketamine on human milk production, its presence in human milk, or effects on the breastfed infant. Esketamine is expected to be excreted to human milk based on published data showing presence of ketamine in cow's milk in cows exposed to intravenously administered ketamine. Advise patients either not to undergo therapy with SPRAVATO while breast feeding or discontinue breast feeding if treatment with SPRAVATO is initiated, taking into account the importance of the drug to the mother.

Fertility

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

4.7 Effects of ability to drive and use machinery

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 Undesirable Effects). Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep (see sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties-Pharmacodynamic effects, Effect on driving).

4.8 Undesirable effects

Clinical Trial Data

Summary of the safety profile

SPRAVATO was evaluated for safety in 1709 patients diagnosed with TRD (patients with MDD and were non-responders to at least two oral antidepressants (ADs), of adequate dosage and duration, in the current major depressive episode) from five Phase 3 studies (3 short term and 2 long term studies) and one Phase 2 dose ranging study. Of all esketamine-treated patients in the completed Phase 3 studies, 479 (29.9%) received at least 6 months of treatment exposure, and 178 (11.1%) received at least 12 months of exposure.

SPRAVATO was evaluated for safety in 262 patients diagnosed with Major Depressive Disorder with suicidal ideation and intent from two Phase 3 studies and one Phase 2 study. Overall, the safety profile of SPRAVATO from this clinical program was generally similar that seen in studies for TRD.

The most commonly observed adverse reactions in patients treated with SPRAVATO (incidence ≥10% and greater than oral AD plus placebo nasal spray) were dissociation, dizziness, nausea, sedation, headache, dysgeusia, hypoaesthesia, vertigo, anxiety, blood pressure increased, and vomiting. Most of these adverse reactions were mild or moderate in severity, reported post dose on the day of administration and resolved the same day.

Tabulated list of adverse reactions

Table 2 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with oral AD plus placebo nasal spray.

Table 2: Adverse Reactions Occurring in TRD patients treated with SPRAVATO Plus Oral AD at any dose and greater than patients treated with oral AD plus placebo nasal spray				
	Double-Blind Population		Open-Label Population	
	SPRAVATO + Oral AD (N=849)	Oral AD + Placebo nasal spray (N=742	SPRAVATO + Oral AD (N=1335)	All SPRAVATO Population (N=1971)
Psychiatric disorders				
Dissociation†	351 (41.3%)	67 (9.0%)	512 (38. 4%)	821 (41.7%)
Anxiety†	108 (12.7%)	54 (7.3%)	161 (12.1%)	271 (13.7%)
Euphoric mood	41 (4.8%)	6 (0.8%)	51 (3.8%)	94(4.8%)
Emotional distress†	26 (3.1%)	4 (0.5%)	33 (2.5%)	61 (3.1%)
Nervous system disorders				
Dizziness†	293 (34.5%)	71 (9.6%)	491 (36.736.8%)	747 (37.9%)
Sedation†	200 (23.6%)	66(8.9%)	321 (24.0%)	510 (25.9%)
Headache†	172 (20.3%)	114 (15.4%)	294 (22.0%)	468 (24.0 23.7%)
Dysgeusia†	170 (20.0%)	88 (11.9%)	207 (15.5%)	350 (17.8%)
Hypoesthesia†	139 (16.4%)	11 (1.5%)	204 (15.3%)	321 (16.3%)
Lethargy†	64 (7.5%)	28 (3.8%)	97 (7.3%)	167 (8.5%)
Mental impairment†	39 (4.6%)	10 (1.3%)	61 (4.6%)	96 (4.9%)
Dysarthria†	21 (2.5%)	2 (0.3%)	37 (2.8%)	59 (3.0%)
Tremor†	19 (2.2%)	11 (1.5%)	28 (2.1%)	52 (2.6%)
Nystagmus	3 (0.4%)	0	10 (0.7%)	13 (0.7%)
Ear and labyrinth disorders				
Vertigo†	133 (19.6 15.7%)	17 (2.3%)	211 (15.8%)	321 (16.3%)
Cardiac disorders				
Tachycardia†	15 (1.8%)	4 (0.5%)	19 (1.4%)	36 (1.8%)
Respiratory, thoracic and mediastinal disorders				
Throat irritation†	71 (8.4%)	32 (4.3%)	117 (8.8%)	183 (9.3%)
Nasal discomfort†	60 (7.1%)	38 (5.1%)	96 (7.2%)	150 (7.6%)
Gastrointestinal disorders				
Nausea	218 (25.7%)	60 (8.1%)	321 (24.0%)	532 (27.0%)
Vomiting	82 (9.7%)	18 (2.4%)	123 (9.2%)	210 (10.7%)
Dry mouth	34 (4.0%)	14 (1.9%)	42 (3.1%)	79 (4.0%)
Salivary hypersecretion	7 (0.0.8%)	1 (0.2%)	5 (0.4%)	11 (0.6%)
Skin and subcutaneous tissue disorders				
Hyperhidrosis†	36 (4.2%)	11 (1.5%)	56 (4.2%)	96 (4.9%)
Renal and urinary disorders				
Pollakiuria†	21 (2.5%)	6 (0.8%)	43 (3.2%)	65 (3.3%)
Dysuria	10 (1.2%)	0	29 (2.2%)	39 (2.0%)
General disorders and administration site conditions				
Feeling drunk	32 (3.8%)	2 (0.3%)	31 (2.3%)	60 (3.0%)
Feeling abnormal	29 (3.4%)	4 (0.5%)	53 (4.0%)	77 (3.9%)
Asthenia	11 (1.3%)	3 (0.4%)	38 (2.8%)	49 (2.5%)
Gait disturbance	5 (0.6%)	2 (0.3%)	6 (0.4%)	11 (0.6%)
Investigations`				
Blood pressure increased†	105 (12.4%)	34 (4.6%)	166 (12.4%)	258 (13.1%)

* Note: The following studies are included in the Double-Blind Population: TRD2003 (Double-Blind Phase), TRD3001, TRD3002, TRD3003 (Maintenance Phase), TRD3005, SUI2001, SUI3001, SUI3002. The following studies are included in the Open-Label Population: TRD2003 (Open-Label Phase), TRD3003 (Induction and Optimisation Data from Direct-Entry patients), TRD3004. The 'All SPRAVATO Population' includes all patients in the SPRAVATO arm in any phase in TRD2003, TRD3001, TRD3002, TRD3003, TRD3004, TRD3005, SUI2001, SUI3001, SUI3002.

† The following terms were combined:
Dissociation includes: dissociation; depersonalisation/derealisation disorder; derealisation; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hallucinations, mixed; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paraesthesia; paraesthesia oral; pharyngeal paraesthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change.
Anxiety includes: anxiety; anticipatory anxiety; anxiety disorder; generalised anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor, psychomotor hyperactivity.
Emotional distress includes: emotional distress; crying; dysphoria**.**
Dizziness includes: dizziness; dizziness postural; procedural dizziness; dizziness exertional.
Sedation includes: sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor.
Headache includes: headache; sinus headache.
Dysgeusia includes: dysgeusia; hypogeusia.
Hypoesthesia includes: hypoesthesia; hypoesthesia oral; hypoesthesia teeth; pharyngeal hypoesthesia; intranasal hypoesthesia.
Lethargy includes: lethargy; fatigue; listless, psychomotor retardation.
Mental Impairment includes: mental impairment; confusional state; disturbance in attention.
Dysarthria includes: dysarthria; speech disorder; slow speech.
Tremor includes: tremor; intention tremor.
Vertigo includes: vertigo; vertigo positional.
Tachycardia includes: sinus tachycardia; tachycardia; heart rate increased; extra-systole.
Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness; nasal pruritus
Throat irritation includes: throat irritation; oropharyngeal pain.
Hyperhidrosis includes: hyperhidrosis; cold sweat.
Pollakiuria includes: pollakiuria; micturition disorder, micturition urgency.
Blood pressure increased includes: blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis.

Long-term safety

Long-term safety of SPRAVATO plus oral AD was assessed in a Phase 3, multicentre, open-label extension study (TRD3008) in 1148 adult patients with TRD representing 3777 patient-years of exposure. Patients were treated with SPRAVATO for a median duration of 45.8 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. Specifically, long-term exposure to esketamine yielded no new trends related to suicidality, abuse potential, increased blood pressure, renal disorders or lower urinary tract symptoms. Additionally, there was no evidence of impaired cognition, interstitial or ulcerative cystitis, or hepatotoxicity. For TRD3008 efficacy data, section 5.1 Pharmacodynamic Properties – Clinical Trials.

Description of selected adverse reactions

Dissociation/perceptual changes

The most common psychological effects of esketamine have been dissociative/perceptual changes (including distortion of time and space and illusions), derealisation and depersonalisation. 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

Adverse reactions of sedation and somnolence 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.

Impaired Cognition

In the short-term studies, treatment with SPRAVATO plus oral AD did not influence any aspect of cognition studied in adult patients with TRD and was not associated with any systematic changes in cognition in the elderly patients. Consistently, in long term studies, performance on each of the

cognitive tests relative to baseline showed slight improvement or remained stable in each treatment phase. In the elderly subgroup (≥65 years of age) slowing of reaction time starting at Week 20 and through the end of the study was observed, however, performance on other cognitive tests remained stable.

Changes 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 receiving SPRAVATO plus oral antidepressants (Table 3).

Table 3: Increases in Blood Pressure in Double-blind, Randomized-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD

	Patients <65 years		Patients ≥65 years	
	SPRAVATO + Oral AD N=346	**Placebo + Oral AD** N=222	**SPRAVATO + Oral AD** N=72	**Placebo + Oral AD** N=65
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%)

Nausea and Vomiting

SPRAVATO can cause nausea and vomiting (Table 4). 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 4).

Table 4: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled, Fixed-dose Study

Treatment (+ Oral AD)		**Nausea**		**Vomiting**	
	N	**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

Nasal Tolerability and Sense of Smell

Across studies, the vast majority of esketamine treated patients had no findings on nasal examination. For the patients who had nasal findings (including nasal discharge, nasal crust, or nasal erythema) all events were of mild severity with the exception of a few moderate findings. The most frequently reported post dose nasal symptoms of moderate or severe intensity (reported in at least 5% of patients) in the Phase 3 studies were post nasal drip, taste disturbance and stuffy nose. Other nasal symptoms of moderate or severe intensity included: runny nose, cough, dryness inside nose and sneezing. In addition, sense of smell was assessed over time; no difference was observed between patients treated with SPRAVATO plus oral AD and those treated with oral AD plus placebo nasal spray during the double-blind maintenance phase of TRD3003.

Body Weight

SPRAVATO had no clinically meaningful effect on body weight over short- or long-term administration. In the double-blind maintenance phase of TRD3003, the proportion of patients with an increase in body weight of ≥7% was comparable for the SPRAVATO plus oral AD vs. oral AD

plus placebo nasal spray groups (13.9% and 13.3%). In the open label, long term study TRD3004, a similar percentage of patients exhibited an increase or decrease in body weight of ≥7% (7.4% and 9.1%, respectively). In TRD3004, mean body weight remained stable during treatment with SPRAVATO plus oral AD both in the induction phase and maintenance phase (mean change from baseline ± standard deviation of -0.29±2.15 kg at Day 28 and 0.44±5.83 kg at Week 48).

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience (Table 5). In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10 (≥10%)
Common	≥ 1/100 and < 1/10 (≥1% and < 10%)
Uncommon	≥ 1/ 1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10000 and < 1/1000 (≥0.01 and < 0.1%)
Very rare	< 1/10000, including isolated reports (< 0.01%).
Not known	Cannot be estimated from the available data

Table 5: Adverse Reactions Identified During Post-marketing Experience with SPRAVATO

System Organ Class Adverse Reaction	**Frequency Category Estimated from Post-marketing Reporting Rates**
Cardiac disorders Bradycardia	Rare
Nervous system disorders Seizure	Rare
Respiratory, thoracic and mediastinal disorders Respiratory Depression	Rare
Vascular disorders Hypotension	Very rare

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

No cases of overdose were reported in clinical studies with SPRAVATO. 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 Dose and Method of Administration).

Symptoms

There is limited clinical trial experience with esketamine nasal spray doses higher than the maximum recommended dose of 84 mg. 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.

Management of overdose

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. ATC code N06AX27.

Putative aetiological contributors of depression, including stress and other conditions, are known to cause structural and functional impairment of synapses in brain regions involved with the regulation of mood and emotional behaviour. Evidence within the literature suggests that 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 that restore synaptic function in these brain regions. Unlike other antidepressant therapies, esketamine's primary antidepressant action does not directly involve monoamine, GABA, or opioid receptors.

Pharmacodynamic effects

Effect on driving

Two studies were conducted to assess the effects of SPRAVATO on driving skills.

In a controlled study in 25 adult subjects with major depressive disorder, driving performance was assessed the day after administration of a single 84 mg dose. Treatment with esketamine nasal spray at this dose did not affect driving performance in a standard driving test.

In a healthy volunteer study (N = 23 subjects), driving performance was assessed 8 hours after administration of a single dose of 84 mg of esketamine nasal spray, mirtazapine, or placebo. The effect of esketamine nasal spray administration on driving was similar to placebo. However, two subjects discontinued the driving test after receiving esketamine because of a perceived inability to drive.

Effect on QT/QTc interval and cardiac electrophysiology

Esketamine did not prolong the QT/QTc interval when nasally administered as an 84 mg dose or when intravenously infused as a 0.8 mg/kg dose over 40 minutes.

Clinical efficacy and safety

Treatment-Resistant Depression

The efficacy and safety of SPRAVATO nasal spray was initially evaluated 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. 1833 adult patients were enrolled, of which 1601 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. Long-term extension study TRD3008 contained 1148 subjects (of which 169 subjects newly received SPRAVATO), who rolled over from studies TRD3001, TRD3002, TRD3003, TRD3004, TRD3005, and TRD3006.

Short-term studies

SPRAVATO was evaluated in three Phase 3 short-term (4-week) randomised, double-blind, multicentre, 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 and SPRAVATO dosages were then maintained on 56 mg or titrated to 84 mg 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) which was maintained or titrated to 56 mg or 84 mg dose administered twice-weekly during a 4-week double-blind induction phase. 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.

The baseline demographic and disease characteristics of patients in TRD3001 and TRD3002 studies were similar between the SPRAVATO plus oral AD and oral AD plus placebo nasal spray groups. The median subject age was 47 years (range 18 to 64 years), 67% were female; 83% Caucasian and 5% of African descent and mean duration of prior AD treatment was approximately 425 days. At the time of screening, the mean duration of the current episode of depression was 168 weeks. At the time of screening, 90% of patients had non-response to ≥2 oral ADs with the remainder requiring confirmation of non-response to the second AD during the 4-week screening prospective phase. The new open label oral AD initiated during the 4-week double blind induction phase was an SSRI in 38% of patients and an SNRI in 62% of patients. In TRD3005, the median subject age was 69 years (range 65 to 86 years) of which, 85% of patients were 65-74 years of age, 62% were female and 95% were Caucasian and mean duration of prior AD treatment was approximately 727 days. At the time of screening, the mean duration of the current episode of depression was 216 weeks in TRD3005. At the time of screening, 85% of patients had non-response to ≥2 oral ADs with the remainder requiring confirmation of non-response to the second AD during the 4-week screening prospective phase. The new open label AD initiated during the 4-week double blind induction phase was an SSRI in 55% of patients and an SNRI in 45% of patients.

The primary efficacy measure was change from baseline in the Montgomery Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression.

In the flexible dose study TRD3002, for the primary efficacy measure of improvement in depressive symptoms (change in MADRS total scores from baseline at the end of the 4-week induction phase), SPRAVATO plus a newly initiated oral AD demonstrated clinically meaningful and statistical superiority compared to standard of care (newly initiated oral AD) plus placebo nasal spray. In studies TRD3001 and TRD3005, 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 standard of care (newly initiated oral AD) plus placebo nasal spray (Table 6). In TRD3002, improvements in the Sheehan Disability Scale (SDS) total score assessing global functional impairment and Patient Health Questionnaire 9 (PHQ 9) total score assessing symptoms of depression numerically favoured SPRAVATO plus a newly initiated oral AD compared to standard of care (newly initiated oral AD) plus placebo nasal spray.

Table 6:	Primary Efficacy Results for Change in MADRS Total Score for 4 Week Clinical Trials (ANCOVA LOCF)				
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)	-18.7 (1.3)	-4.1 (-7.5, -0.6)[#]
	SPRAVATO 84 mg + oral AD	114	37.8 (5.6)	-17.3 (1.3)	-2.0 (-5.5, 1.4)[#]
	Oral AD + Placebo nasal spray	113	37.5 (6.2)	-14.8 (1.3)	
TRD3002	SPRAVATO (56 mg or 84 mg) + oral AD	114	37.0 (5.7)	-18.0 (1.3)	-3.5 (-6.7, -0.3)[‡]
	Oral AD + Placebo nasal spray	109	37.3 (5.7)	-14.5 (1.3)	
TRD3005 (≥65 years)	SPRAVATO (28 mg, 56 mg or 84 mg) + oral AD	72	35.5 (5.9)	-10.9 (1.7)	-3.6 (-7.2, -0.03)[#]
	Oral AD + Placebo nasal spray	65	34.8 (6.4)	-6.9 (1.7)	

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

§ Nasally administered esketamine or placebo; oral AD=standard of care (newly initiated AD)

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

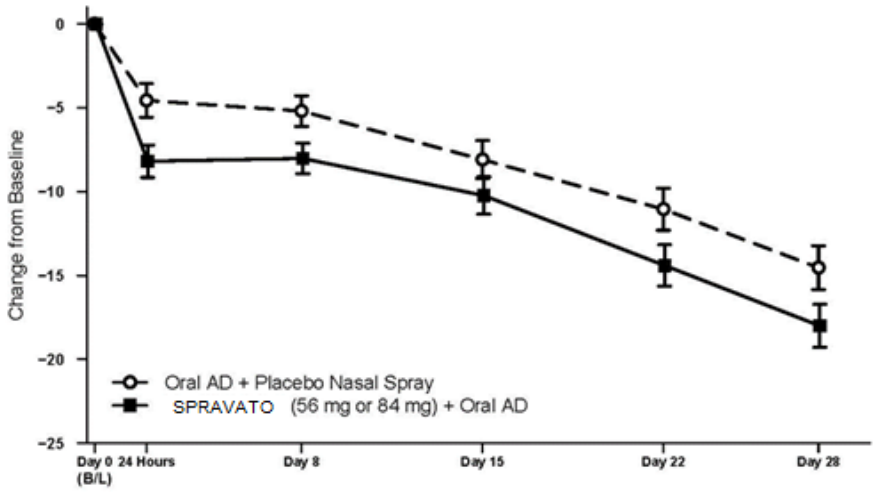
‡ Treatment groups that were statistically significantly superior to oral AD + placebo nasal spray

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

Time Course of Treatment Response

In Study TRD3002, an effect of SPRAVATO on symptom reduction was observed as early as 24 hours post-dose and increased in subsequent weeks with the full antidepressant effect of SPRAVATO seen by Day 28. Throughout the 4-week double blind induction phase of Study TRD3002, the mean change in MADRS total score for flexibly dosed SPRAVATO (56 mg or 84 mg) plus oral AD was greater than for oral AD plus nasally-administered placebo. At Day 28, 67% of the patients randomised to SPRAVATO were on 84 mg. Figure 1 depicts time course of response in the primary efficacy measure (MADRS) in Study TRD3002. A consistent treatment effect was observed in Studies TRD3001 and TRD3005.

Figure 1: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Study TRD3002* (Full Analysis Set) – ANCOVA LOCF Analysis with Standard Error Bars



* Note: In this flexible-dose study, dosing was individualised based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO™ dose from 84 mg to 56 mg, and almost all remained on the lower dose for the duration of the induction phase.

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 7)

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 7).

Table 7: Response and Remission Rates in 4 Week Clinical Trials Based on LOCF 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 (19.0%)	21 (18.3%)	30 (26.1%)	52 (45.2%)	61 (53.0%)	40 (34.8%)
	SPRAVATO 84 mg + oral AD	17 (16.3%)#	16 (14.3%)	26 (23.2%)	35 (31.0%)	54 (47.8%)	40 (35.4%)
	Oral AD + Placebo nasal spray	8 (7.9%)	5 (4.4%)	15 (13.3%)	27 (23.9%)	42 (37.2%)	33 (29.2%)
TRD3002	SPRAVATO 56 mg or 84 mg + oral AD	18 (16.5%)	15 (13.4%)	29 (25.9%)	54 (48.2%)	71 (63.4%)	54 (48.2%)
	Oral AD + placebo nasal spray	11 (10.8%)	13 (11.9%)	23 (21.1%)	36 (33.0%)	54 (49.5%)	33 (30.3%)
TRD3005 (≥65 years)	SPRAVATO 28 mg, 56 mg or 84 mg + oral AD	NA	4 (6.1%)	4 (5.6%)	9 (12.7%)	17 (23.9%)	11 (15.5%)
	Oral AD + placebo nasal spray	NA	3 (4.8%)	8 (12.5%)	10 (15.6%)	8 (12.5%)	4 (6.3%)

AD=antidepressant; NA=not available

§ Nasally administered SPRAVATO or placebo; oral AD=standard of care (newly initiated AD)

† 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

Study TRD3003 (SUSTAIN-1) – Relapse-prevention study

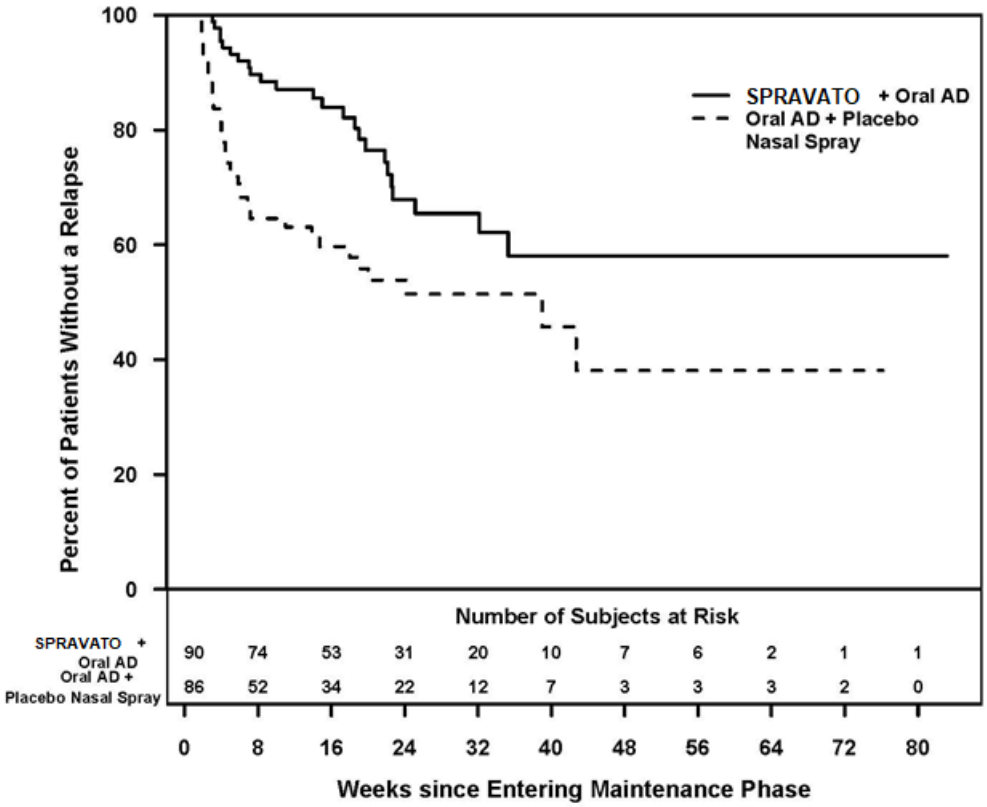
Study SUSTAIN-1 (TRD3003) was a long-term randomised, double-blind, parallel-group, active-controlled, multicentre, relapse prevention study. Overall a total of 705 patients were enrolled; 437 directly enrolled; 150 transferred from TRD3001, and 118 transferred from TRD3002. Patients directly enrolled were administered SPRAVATO (56 mg or 84 mg twice weekly) plus oral AD in a 4-week open label induction phase. Patients who were responders (MADRS total score reduction ≥50% from baseline), continued receiving treatment with SPRAVATO plus oral AD in a 12-week optimisation 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). Four hundred fifty-five (455) esketamine-treated patients entered the optimisation phase, patients in stable remission or stable response were randomised to continue with SPRAVATO or stop SPRAVATO and switch to placebo nasal spray. After an initial 16 weeks of treatment with SPRAVATO plus oral AD, 176 (39%) patients were in stable remission and 121 (27%) patients were in stable response (but not in stable remission). 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.

The baseline demographic and disease characteristics of the patients randomised to the double-blind maintenance phase were similar between the SPRAVATO plus oral AD and oral AD plus placebo groups, median patient age was 48 years (range 19 to 64 years), 66% were female; 90% Caucasian and 4% of African descent.

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 standard of care (oral AD) plus placebo nasal spray (Figure 2). 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 standard of care (oral AD) 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 2: Time to Relapse in Patients in Stable Remission in Study TRD3003 (Full Analysis Set)

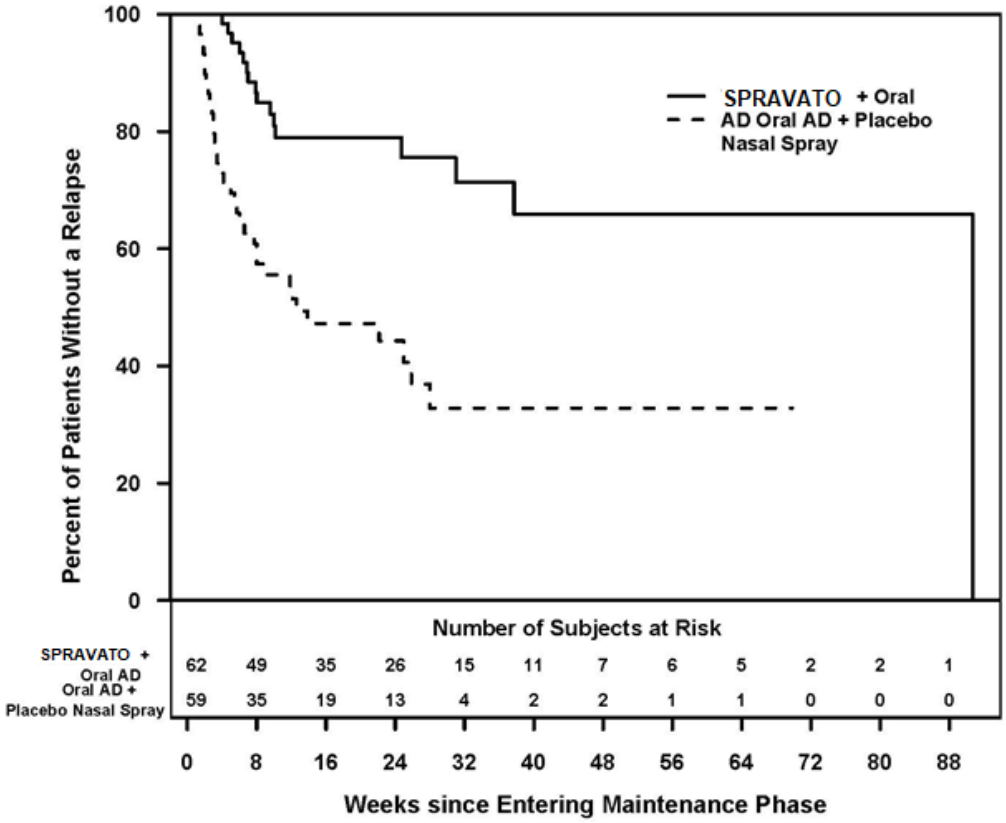


For patients in stable remission, the estimated hazard ratio (95% CI) of SPRAVATO plus oral AD relative to standard of care (oral AD) plus placebo nasal spray based on weighted estimates was 0.49 (95% CI: 0.29, 0.84), indicating that, patients who were in stable remission and continued treatment with SPRAVATO plus oral AD group were on average 51% less likely to relapse than patients who switched to standard of care (oral AD) plus placebo nasal spray.

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 standard of care (oral AD) plus placebo nasal spray (Figure 3). The median time to relapse for standard of care (oral AD) plus placebo nasal spray group (88 days) was shorter compared to SPRAVATO plus oral AD group (635 days).

Figure 3: Time to Relapse in Patients in Stable Response in Study TRD3003 (Full Analysis Set)



For patients in stable response, the estimated hazard ratio (95% CI) of SPRAVATO plus oral AD relative to standard of care (oral AD) plus placebo nasal spray based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55), indicating that, patients who were stable responders and continued treatment with SPRAVATO plus oral AD group were on average 70% less likely to have a relapse than patients who switched to standard of care (oral AD) plus placebo nasal spray.

Enrolment 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

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. The dosing frequency used the majority of the time during the maintenance phase is shown in Table 8. Of the patients randomised to SPRAVATO, 60% received 84 mg and 40% received 56 mg dose.

Table 8: 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 TRD3004 (SUSTAIN-2) – Open-label Long-term Safety and Efficacy Study

Study SUSTAIN-2 (TRD3004) was an open-label, long-term study of SPRAVATO plus oral AD in patients with TRD.

The primary objective was to evaluate the long-term (up to 52 weeks) safety and efficacy of SPRAVATO. SPRAVATO was not associated with effects on cognitive function or treatment-emergent symptoms of interstitial cystitis. In the elderly subgroup (≥65 years of age) slowing of reaction time starting at Week 20 and through the end of the study was observed, however, performance on other cognitive tests remained stable.

In addition, there was no evidence of withdrawal and/or rebound symptoms following cessation of SPRAVATO treatment. No cases of respiratory depression were reported and there was no evidence of treatment related changes in lab parameters.

Mean body weight remained stable during treatment with SPRAVATO plus oral AD both in the induction phase and maintenance phase (mean change from baseline ± standard deviation of -0.29±2.15 kg at Day 28 and 0.44±5.83 kg at Week 48).

TRD3004 also evaluated long-term efficacy, including effects on depressive symptoms. At the end of the 4-week induction phase, the response rate (≥50% improvement from Baseline in the MADRS total score) was 78.4% (593/756) and remission rate (MADRS total score ≤12) was 47.2% (357/756); of the responders proceeding to the maintenance phase, 76.5% (461/603) were in response and 58.2% (351/603) were in remission at endpoint.

Study TRD3008 (SUSTAIN-3) – Open-label Long-Term Extension Study

Study SUSTAIN-3 (TRD3008) was a Phase 3, multicentre, open-label extension study of SPRAVATO plus oral AD in 1148 adult patients with TRD representing 3777 patient-years of exposure.

The primary objective of this study was to assess the long-term safety and tolerability of SPRAVATO in patients with TRD. No new safety concerns were identified (see section 4.8 Undesirable Effects – Long-term Safety).

TRD3008 also evaluated long-term efficacy. During the 4-week induction phase, patients showed in general an improvement in measures of depressive symptoms, functioning, and health-related quality of life. The effects appeared to be maintained during the optimisation/maintenance phase for up to 79 months, with approximately half of patients in remission during most MADRS assessments in this phase.

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 9) and key secondary (Table 10) efficacy measure.

Table 9: 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%)
Difference in percentage (95% CI)	9.44 (3.19, 15.68)	–
Adjusted odds ratio (95% CI)	1.74 (1.20, 2.52) P = 0.003[b]	–

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] P-value for Cochran–Mantel–Haenszel (CMH) test, adjusting for age groups (18-64; ≥65) and total number of treatment failures.

Table 10: 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%)
Difference in percentage (95% CI)	7.61 (1.85, 13.37)	–
Adjusted odds ratio (95% CI)	1.72 (1.15, 2.57) P = 0.008[b]	–

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

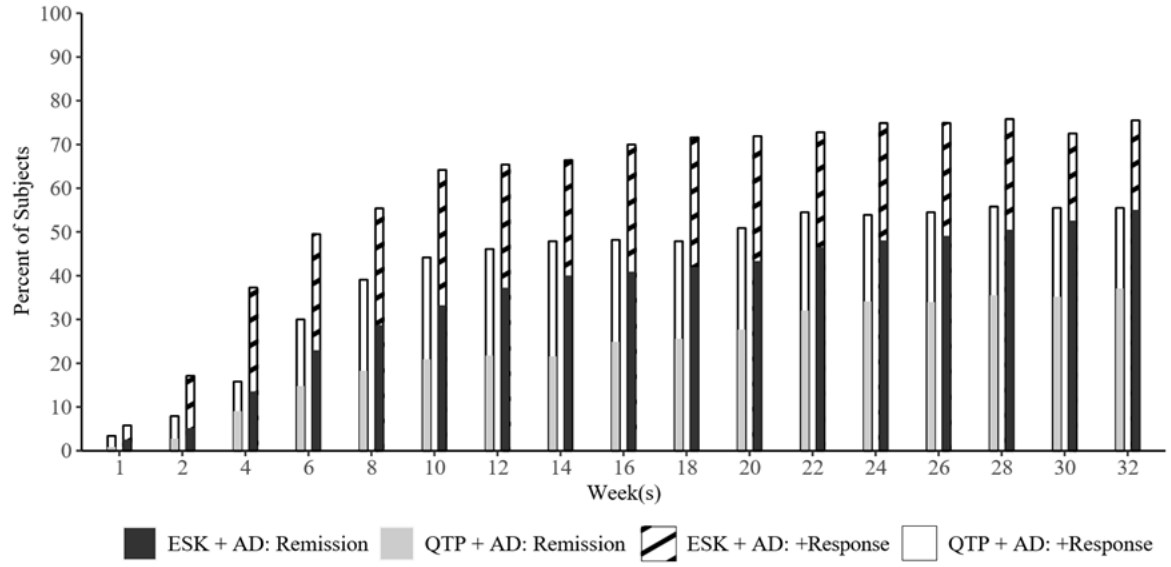
[a] A patient who discontinued study intervention was considered as a negative outcome. For patients for whom no MADRS result was available at the Week 8 visit but who did not discontinue study intervention or withdraw from study before Week 8, LOCF of MADRS was applied.

[b] P-value for CMH test, adjusting for age groups (18-64; ≥65) and total number of treatment failures.

Remission and Response Rates

Rate of remission at Week 32 was 55.0% for patients in the SPRAVATO plus oral AD group and 37.0% in the quetiapine XR plus oral AD group, with an odds ratio (95% CI) of 2.09 (1.53, 2.85). Rate of response (defined as ≥ 50% reduction in the MADRS total score from baseline or MADRS total score is ≤ 10) at Week 32 was 75.5% for patients in the SPRAVATO plus oral AD group and 55.5% in the quetiapine XR plus oral AD group, with an odds ratio (95% CI) of 2.48 (1.78, 3.46). Figure 4 depicts the percentage of patients in remission and/or in response in the Treatment phase.

Figure 4: Percentage of Patients in Remission and/or in Response (LOCF) in Study TRD3013, Treatment Phase; Full Analysis Set



Percentages are based on the number of patients in the indicated population at each timepoint.
Remission is defined as a MADRS total score of ≤10.
A patient is defined as a responder at a given time point if the percent improvement in MADRS total score from baseline is ≥50% or if the MADRS total score is ≤10.

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.

Dose-response study in treatment-resistant depression

A Phase 2 adjunctive, doubly-randomised, double-blind, placebo-controlled, dose-ranging study, enrolled 108 adult patients with TRD. Adjunctive to continued oral AD therapy, patients were treated with esketamine 14 mg, 28 mg, 56 mg or 84 mg or placebo administered nasally twice a week for 2 weeks. Treatment with the 28-mg, 56-mg and 84-mg doses of SPRAVATO significantly improved depressive symptoms in patients with TRD as demonstrated by the change in MADRS total score after 1 week. While SPRAVATO doses of 28 mg, 56 mg and 84 mg were efficacious in TRD treatment, the duration of the efficacy of the 28-mg dose was shorter.

Response rates at Day 8 of Period 1 for the double-blind phase are shown below (Table 11).

Table 11: Response Rates in TRD2003 (Double Blind Phase – Period 1)

		Number of Patients (%)		
		Response Rate†		
	Treatment Group§	2 hours	24 hours	Day 8
Panel A	SPRAVATO 28mg	6 (54.5%)	4 (36.4%)	1 (9.1%)
	SPRAVATO 56 mg	4 (36.4%)	3 (27.3%)	2 (18.2%)
	SPRAVATO 84 mg	7 (58.3%)	5 (41.7%)	5 (41.7%)
	Placebo Nasal Spray	6 (18.2%)	1 (3.0%)	2 (6.1%)
Panel B	SPRAVATO 14mg	4 (36.4%)	4 (36.4%)	2 (18.2%)
	SPRAVATO 56 mg	4 (44.4%)	4 (44.4%)	2 (22.2%)
	Placebo Nasal Spray	7 (33.3%)	6 (28.6%)	5 (23.8%)

§ Nasally administered SPRAVATO or placebo
† Response was defined as ≥50% reduction in the MADRS total score from baseline

Major Depressive Disorder with acute suicidal ideation or behaviour

SPRAVATO was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, Aspire I (SUI3001; NCT03039192) and Aspire II (SUI3002; NCT03097133) in adult patients with moderate to severe MDD (MADRS total score >28) who had active suicidal ideation with intent. In these studies, patients received treatment with SPRAVATO84 mg or placebo nasal spray twice-weekly for 4 weeks. All patients received comprehensive standard of care (SOC) treatment, including an initial inpatient hospitalization and a newly initiated or optimized oral antidepressant (AD) therapy (AD monotherapy or AD plus augmentation) as determined by the investigator. After the first dose, a one-time dose reduction to SPRAVATO 56 mg was allowed for patients unable to tolerate the 84 mg dose.

The baseline demographic and disease characteristics of patients in SUI3001 and SUI3002 were similar between the SPRAVATO plus SOC or placebo nasal spray plus SOC 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 regimen, and 6% received both AD monotherapy/AD plus augmentation regimen.

The primary efficacy measure was the reduction of symptoms of MDD as measured by the change from baseline MADRS total score at 24 hours after first dose (Day 2).

In SUI3001 and SUI3002, SPRAVATO plus SOC demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus SOC (see Table 12).

Table 12: Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies SUI3001 and SUI3002) (ANCOVA*)

Study No.	Treatment Group[§]	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline to 24 hr Post First Dose (SE)	LS Mean Difference (95% CI)[†] p-value
SUI3001	SPRAVATO 84 mg + SOC	111	41.3 (5.87)	-15.9 (1.04)	-3.8 (-6.56; -1.09)[‡] P=0.006
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.0 (1.02)	-
SUI3002	SPRAVATO 84 mg + SOC	113	39.4 (5.21)	-16.0 (1.02)	-3.9 (-6.60; -1.11) [‡] P=0.006
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.2 (1.05)	-
Pooled Studies (SUI3001 and SUI3002)	SPRAVATO 84 mg + SOC	224	40.3 (5.61)	-16.0 (0.72)	-3.8 (-5.75; -1.89) [‡]
	Placebo nasal spray + SOC	225	40.4 (6.04)	-12.1 (0.72)	-

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

* ANCOVA LOCF: For SUI3001, 1 subject (in the placebo + SOC group) did not have the Day 2 (24 hours post first dose) MADRS total score, and the MADRS total score was carried forward from 4 hours after the first dose. For SUI3002, of the 6 subjects who did not have the Day 2 (24 hours post first dose) MADRS total score, 5 of them were able to carry the MADRS total score from 4 hours after the first dose.

§ Nasally administered esketamine or placebo.

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

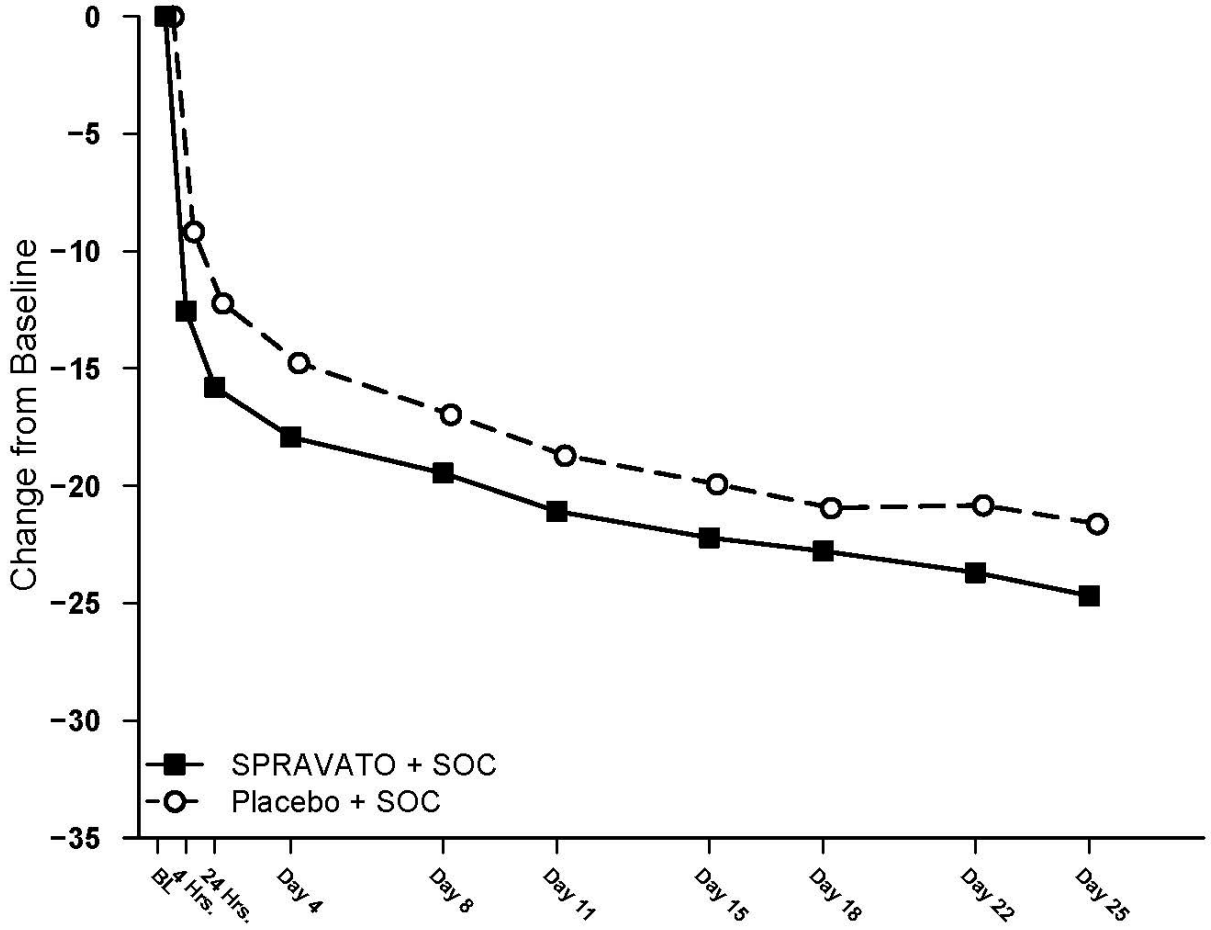
‡ Treatment groups that were statistically significantly superior to placebo nasal spray + SOC.

The treatment differences (95% CI) in change from baseline in MADRS total score at Day 2 (24 hours post first dose) between SPRAVATO + SOC and placebo + SOC were -4.81 (-7.26; -2.36) for the subpopulation that reported a prior suicide attempt (N=282) and -2.32 (-5.54; 0.91) for the subpopulation that did not report a prior suicide attempt (N=166).

Time Course of Treatment Response

In both SUI3001 and SUI3002, 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 5 depicts time course of the primary efficacy measure of change in MADRS total score using pooled SUI3001 and SUI3002.

Figure 5: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in SUI3001 and SUI3002 * (Pooled, Full Analysis Set) – MMRM



* Note: In these studies, 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 16% of patients had reduction in SPRAVATO dosage from 84 mg to 56 mg twice weekly.

Remission rates

In the Phase 3 studies, the percentage of patients who achieved remission (MADRS total score ≤12 at any given time during the study) was greater in the SPRAVATO + SOC group than in the placebo + SOC group at all timepoints during the double-blind treatment phase (Table 13). At the double-blind endpoint (Day 25, 4 hours postdose), remission rates were 50% in the esketamine + SOC group and 37% in placebo + SOC group based on the prespecified criteria of MADRS total score ≤12.

Table 13: Patients Who Achieved Remission of MDD; Double-blind Treatment Phase; Full Efficacy Analysis Set

	SUI3001		SUI3002		Pooled Studies (SUI3001 and SUI3002)	
	Placebo + SOC 112	SPRAVATO + SOC 112	Placebo + SOC 113	SPRAVATO + SOC 114	Placebo + SOC 225	SPRAVATO + SOC 226
Day 1, 4 hours post first dose Patients with Remission of MDD	9 (8.0%)	12 (10.7%)	4 (3.5%)	12 (10.5%)	13 (5.8%)	24 (10.6%)
Day 2, 24 hours post first dose Patients with Remission of MDD	10 (8.9%)	21 (18.8%)	12 (10.6%)	25 (21.9%)	22 (9.8%)	46 (20.4%)
Day 25 Patients with Remission of MDD	38 (33.9%)	46 (41.1%)	31 (27.4%)	49 (43.0%)	69 (30.7%)	95 (42.0%)
Day 25, 4 hour postdose Patients with Remission of MDD	42 (37.5%)	60 (53.6%)	42 (37.2%)	54 (47.4%)	84 (37.3%)	114 (50.4%)

SOC = standard of care
Note: Remission is based on a MADRS total score of ≤12. Subjects who did not meet such criterion or discontinued prior to the time point for any reason are not considered to be in remission.

Effects on Suicidality

Overall patients in both treatment groups experienced improvement in the severity of their suicidality as measured by the Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-r) scale at the 24-hour endpoint, though there was no statistically significant difference between treatment groups. The long-term efficacy of SPRAVATO to prevent suicide has not been established.

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 and Method of Administration).

Dose-dependent, linear increases in the plasma C_{max} and 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 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.

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, respectively, 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.

Renal Impairment

Relative to the subjects with normal renal function (creatinine clearance [CLCR], 88 to 140 mL/min), the C_{max} of esketamine was on average 20 to 26% higher in subjects with mild (CLCR, 58 to 77 mL/min), moderate (CLCR, 30 to 47 mL/min), or severe (CLCR, 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.

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. Both parameters were approximately 40% higher in Japanese subjects, relative to Caucasian subjects. On average, esketamine C_{max} was 10% lower and AUC_{∞} was 17% greater in Korean subjects, relative to Caucasian 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

A population pharmacokinetic analysis was conducted that included healthy subjects (138 males and 118 females) and patients with major depressive disorder (203 males and 361 females). The results indicated that the pharmacokinetics of esketamine administered as a nasal spray is not influenced by gender.

Body Weight

A population pharmacokinetic analysis was conducted that included 256 healthy subjects and 564 patients with major depressive disorder. The total body weight of the subjects ranged from 39 to 170 kg. The results indicated that the pharmacokinetics of esketamine administered as a nasal spray is not influenced by body weight.

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

General Toxicity

Once daily nasal 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 non-adverse central nervous system related clinical signs reflecting the anaesthetic properties of the test article. No notable lesions were found in the nasal cavity or any peripheral organ. After 3 months of daily treatment at 9 mg/day in rats, the systemic exposure of esketamine (C_{max} and AUC) resembled that in humans at the maximum recommended human dose (MRHD) of 84 mg, while the C_{max} and AUC based exposure ratios for esketamine in dogs after 3 months of daily treatment at 72 mg/day were approximately 4- and 1- fold, respectively.

Neurotoxicity

In single dose and 14-day repeated dose neurotoxicity studies with nasally administered esketamine in rats, no histopathological brain lesions were noted. In single dose neurotoxicity studies, where rats were nasally administered with 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, compared to the human exposure at the MRHD of 84 mg. In a 14-day neurotoxicity study where rats received nasally 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. Moreover, no evidence of neurotoxicity was found in the 6-month rat and the 9-month dog repeated dose toxicology studies with once daily nasal administration of esketamine as judged by brain histopathology and functional assessments. Similarly, no neurotoxicity was noted in the shorter-term animal toxicology studies with nasally administered esketamine. Overall, the risk of neurotoxicity associated with nasal administration of esketamine to patients is expected to be low.

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. In simulated gastric fluid there is no evidence that N-nitroso esketamine is formed out of the fraction of the nasally administered dose of esketamine that is orally absorbed.

Carcinogenicity and Mutagenicity

Once daily nasal administration of esketamine did not increase the incidence of tumours in a 2-year rat carcinogenicity study at doses up to 9 mg/day. At this dose, the exposure to esketamine resembled the human exposure at the MRHD of 84 mg. Esketamine was not carcinogenic either upon once daily subcutaneous administration in a 6 month study in transgenic (Tg.rasH2) mice at doses up to 70/40 mg/kg/day. At that dose, the C_{max}-and AUC- based exposure ratios for esketamine were approximately 20- and 4-fold, respectively, compared to the MRHD of 84 mg.

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 up to 150 mg/kg/day. In rats, the C_{max}- and AUC-based safety margin estimated for esketamine at the 150 mg/kg/day dose of ketamine was 61- and 12-fold compared to the maximum recommended human dose (MRHD) of esketamine of 84 mg. In pregnant rabbits, racemic ketamine was administered intranasally from gestational day 6 to 18 at doses of 10,30, and 100mg/kg/day. The high dose was lowered from 100 to 50mg/kg after 5 days of dosing due to excessive mortality in the pregnant rabbits. Skeletal malformations were observed at doses ≥ 30 mg/kg/day, which were maternally toxic. In rabbits, the estimated exposure to esketamine at the 10 mg/kg/day no effect dose of ketamine was below the maximum exposure to esketamine at 84 mg in humans.

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 Fertility, Pregnancy and Breastfeeding).

In a pre- and postnatal developmental toxicity study with nasally-administered esketamine up to 9 mg/day in rats, no adverse effects occurred in the dams nor their offspring.

Fertility

In a fertility and early embryonic developmental toxicity study, esketamine nasally administered to rats at 0.9, 3, or 9 mg/day caused maternal and paternal toxicity at 3 and 9 mg/day. Fertility and reproductive capacities were not adversely affected at any dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Disodium edetate

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

SPRAVATO nasal spray has a 48-month shelf-life.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Clear and colourless to slightly yellowish solution free from visible particles in a type-I glass vial with rubber stopper assembled into a single-use nasal spray device.

SPRAVATO is provided in cartons containing 1, 2 or 3 single-use nasal spray devices.

6.6 Special precautions for disposal and handling

The treatment site will arrange for disposal of any unused medicine or waste material. No special requirements. See Instructions for Use for handling of product.

7. MEDICINE SCHEDULE

Controlled Drug (C4)

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND
Telephone: 0800 800 806
FAX: (09) 588 1398
Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

19 December 2019

10. DATE OF REVISION OF THE TEXT

13 January 2025

Summary table of changes

Section changes	Summary of new information
4.8	Addition of seizures and bradycardia as adverse reaction
4.4, 4.8, 5.1	Addition of data from SUSTAIN-3 (TRD3008) and ESCAPE-TRD (TRD3013) studies