Summary Report of Benefit-Risk Assessment

SPRAVATO (ESKETAMINE) NASAL SPRAY 28MG

NEW DRUG APPLICATION

Active Ingredient(s)	Esketamine
Product Registrant	Johnson and Johnson Pte Ltd
Product Registration Number	SIN16033P
Application Route	Abridged evaluation
Date of Approval	27 Oct 2020

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A INTRODUCTION

Spravato, in combination with an oral antidepressant (selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI)), is indicated for treatment-resistant depression (TRD). TRD is defined as Major Depressive Disorder (MDD) in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode.

The active substance, esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. Through NDMA-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 brain regions involved with the regulation of mood and emotional behaviour. Esketamine is classified as a Class A Controlled Drug under the Misuse of Drugs Act.

Spravato is available as a single-use nasal spray containing 28 mg/vial of esketamine as esketamine hydrochloride. Other ingredients in the nasal spray are citric acid monohydrate, edetate disodium, sodium hydroxide and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, esketamine hydrochloride, is manufactured at Janssen Pharmaceuticals, Inc, Athens, GA, USA and CU Chemie Uetikon GmbH, Lahr, Germany. The drug product, Spravato Nasal Spray 28mg/vial, is manufactured at Renaissance Lakewood LLC, New Jersey, USA.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for Janssen Pharmaceuticals, Inc, Athens, GA, USA were adequate to support the approved storage condition and re-test period. The packaging is double, antistatic, low-density polyethylene (LDPE) bags (i.e. an inner and an outer bag), which are closed appropriately with a twist-tie or equivalent. The drug substance is approved with a re-test period of 36 months and no special storage condition is required.

The stability data presented for CU Chemie Uetikon GmbH, Lahr, Germany are adequate to support the approved storage condition and re-test period. The packaging is polyethylene bags

placed in polyethylene drums. The drug substance is approved with a re-test period of 60 months and no special storage condition is required.

Drug product:

The nasal spray is manufactured by mixing and filling into the container closure system. The process is considered to be a standard manufacturing process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 24 months when stored at or below 30 ºC. The container closure system is Type-1 glass vial with rubber stopper, assembled into a manually activated single-use nasal spray device.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of esketamine in conjunction with an oral antidepressant (AD) for TRD was based primarily on data from 4 pivotal studies, namely the short-term studies TRD3001, TRD3002 and TRD3005, and a long-term study, TRD3003.

Studies TRD3001, TRD3002 and TRD3005 were Phase III randomised, double-blind placebo controlled, short-term studies in adults (TRD3001, TRD3002: 18-64 years; TRD3005: ≥ 65 years) who had moderate to severe depression and had not responded to 2 or more different oral AD for the current depression episode. In each study, there was a screening/observational phase of 4 to 7 weeks, followed by a 4-week randomised double-blind induction phase and a follow-up post-treatment phase (TRD3001, TRD3002: 24 weeks; TRD3005: 2 weeks). During the induction phase, patients received their randomised intranasal treatment twice-weekly concomitantly with a newly initiated once-daily oral AD (SSRI or SNRI).

In study TRD3001, patients were randomised 1:1:1 to receive esketamine 56 mg, 84 mg or placebo in a fixed-dose regimen. Subjects randomised to the esketamine 84 mg arm were given a starting dose of 56 mg on Day 1, and then increased to 84 mg on Day 4. Subjects randomised to the 56 mg arm remained on the assigned dose throughout the induction phase. In study TRD3002, patients were randomised 1:1 to esketamine 56 mg/84 mg or placebo in a flexible-dose regimen, and those treated with esketamine were given a starting dose of 56 mg and titrated upwards to 84 mg based on clinical response. In study TRD3005, elderly patients were randomised 1:1 to esketamine or placebo in a flexible-dose regimen. Esketamine was initiated at a lower dose of 28 mg to improve tolerability, and titrated up to 56 mg or 84 mg depending on clinical response.

The primary endpoint in the 3 short-term studies was the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to the end of the 4-week double-blind induction phase (Day 28). The key secondary endpoints were onset of clinical response (defined as at least 50% improvement from baseline in the MADRS score by Day 2 that is maintained to Day 28; studies TRD3001 and TRD3002 only), change from baseline to the end of induction phase in Sheehan Disability Scale (SDS) (functioning and associated disability) and Patient Health Questionnaire 9-item (PHQ-9) total score (depression symptoms). Other secondary endpoints included remission (defined as MADRS total score ≤12) and response rate (≥50% reduction in MADRS score from baseline). In the fixed-dose study, TRD3001, a truncated fixed sequence parallel gatekeeping approach was applied to adjust for multiplicity across the primary and 3 key secondary endpoints and the 2 dose-vs-control comparisons, whereby the endpoints were tested in the aforementioned order and for all 4 endpoints, the esketamine 56 mg arm would be tested only if statistical significance of that endpoint was shown for the 84 mg arm. In study TRD3002, a serial gatekeeping approach was similarly applied to adjust for multiplicity across the primary and 3 key secondary endpoints in the same order as in study TRD3001.

Across the 3 short-term studies, a total of 711 subjects were randomised to receive esketamine or placebo. Overall baseline demographics were similar between treatment arms in Study 3001 and 3002. The median subject age was 47 years, 67% were female, 83% Caucasian and the mean duration of the current episode of depression was 168 weeks. At the time of screening, 90% of patients had nonresponse to ≥2 oral ADs, with the remainder requiring confirmation of non-response to the second AD during the 4-week screening prospective phase. In Study 3005, the median subject age was 69 years of which 85% of patients were 65-74 years of age, 62% were female, 95% Caucasian and the mean duration of the current episode of depression was 216 weeks. 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.

In study TRD3001, reductions in the MADRS score from baseline compared to placebo were observed in both the esketamine 84 mg and 56 mg arms. However, the difference between esketamine 84 mg and placebo was not statistically significant (mean difference -3.2; 95% CI -6.9, 0.5; 2-sided p-value=0.088). In accordance with the predefined testing sequence, esketamine 56 mg vs placebo could not be formally evaluated, although there was a numerical improvement in MADRS score of -4.1 compared to placebo. The lack of statistical significance for esketamine 84 mg arm in TRD3001 may be attributed to a higher rate of discontinuations in the esketamine 84 mg arm compared to the 56 mg and placebo arms (16.4%, 5.1% and 5.3% respectively). The majority of discontinued subjects in the 84 mg group (11 of 19 subjects) discontinued after the first dose of 56 mg, and these subjects did not go on to receive the subsequent doses of 84 mg while in the study. Furthermore, there was a relatively high placebo response (-14.8 reduction in MADRS score from baseline) which could be attributed to expectation bias by patients and the concurrent use of a newly-initiated AD. Improvements were shown for the key secondary endpoints, although formal statistical evaluations were not performed. The proportion of patients achieving onset of clinical response was 10.4% and 8.8% for esketamine 56 mg and 84 mg, respectively, vs 1.8% in the placebo arm. Numerical improvements in functioning, associated disability and depression symptoms (SDS and PH-9), remission rates and response rates relative to placebo were also observed.

In the flexible-dose study, TRD3002, the primary endpoint was met as the difference between esketamine and placebo was statistically significant (mean difference -4.0; 95% CI -7.3, -0.6; 2-sided p value=0.020). The proportion of patients achieving onset of clinical response for

esketamine compared to placebo was 7.9% vs 4.6% and the difference was not statistically significant (odds ratio 1.79; 95% CI 0.57, 5.67; p>0.025). Numerical improvements in patient-reported symptoms and functioning (SDS and PH-9), remission rates and response rates relative to placebo were also observed. The majority of subjects (66.7%) were titrated to esketamine 84 mg by Day 25, which supports the flexible-dosing regimen of up to 84 mg.

In the study in elderly patients, TRD3005, the difference in MADRS score reduction from baseline between the esketamine group and placebo group was not statistically significant (mean difference -3.6; 95% CI -7.2, 0.1; 2-sided p value=0.059). This could be attributed to a lower starting dose of esketamine 28 mg given to elderly patients in order to improve tolerability. Despite the initial low dose, the improvement over placebo observed in this study by Day 28 was comparable to the that observed in studies TRD3001 and TRD3002 (-3.2 to -4.1). Numerical improvements in the esketamine arm relative to placebo were also observed for the secondary endpoints. Esketamine demonstrated a higher response rate (27.0% vs 13.3%) and remission rate (17.5% vs 6.7%) compared to the placebo group by Day 28. The majority of subjects (64.5%) assigned to the esketamine group were on 84 mg by Day 25.

Summary of Primary Endpoint Results in Phase III Short-Term Studies (Change in MADRS Total Score from Baseline to Day 28, MMRM Analysis)

Study TRD3001	**Placebo (N=113)**	**ESK 84 mg (N=114)**	**ESK 56 mg (N=115)**
LS mean CFB to Day 28			
N	108	98	111
Mean (SE)	-14.8 (1.3)	-18.5 (1.4)	-18.8 (1.3)
Comparison with placebo			
LS Mean Difference	-	-3.2	-4.1
95% CI	-	-6.9, 0.5	-7.7, -0.5
2-sided p-value	-	0.088 (NS)	NA*

Study TRD3002	**Placebo (N=109)**	**ESK 56/84 mg (N=114)**
LS mean CFB to Day 28		
N	100	101
Mean (SE)	-15.8 (1.3)	-19.8 (1.3)
Comparison with placebo		
LS Mean Difference	-	-4.0
95% CI	-	-7.3, -0.6
2 sided p-value	-	0.020

Study TRD3005	**Placebo (N=65)**	**ESK 28 mg, 56/84 mg (N=72)**
LS mean CFB to Day 28		
N	60	63
Mean (SE)	-6.2 (1.5)	-10.2 (1.5)
Comparison with placebo		
LS Mean Difference	-	-3.6
95% CI	-	-7.2, 0.1
2 sided p-value	-	0.059 (NS)

ESK: esketamine; CFB: change from baseline; SR: standard error; LS mean: least squares mean; CI: confidence interval; NS: not statistically significant

*In accordance with the predefined testing sequence, esketamine 56mg vs placebo could not be formally evaluated

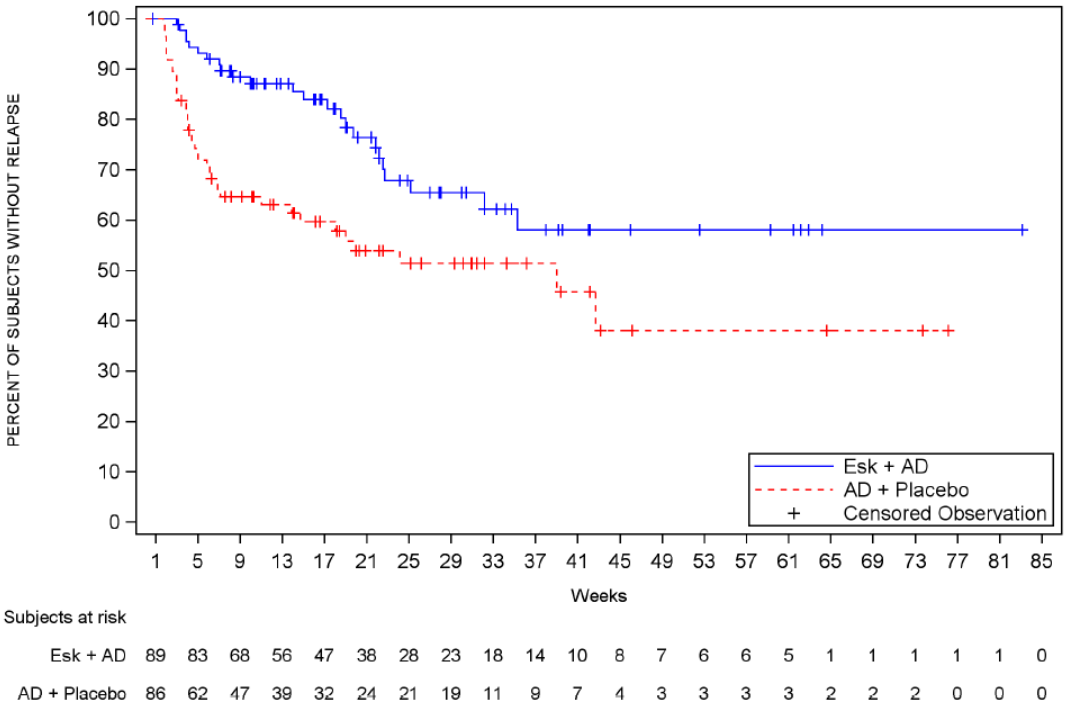
Study TRD3003 was a long-term randomised, double-blind, parallel group, active-controlled, multicentre, relapse prevention study in adults who had achieved stable remission or stable response with esketamine and concomitant oral AD. A total of 705 patients were enrolled, comprising 437 who were directly enrolled, and a further 150 and 118 patients who were enrolled from Study TRD3001 and Study TRD3002, respectively. Direct-entry patients underwent a 4-week screening phase, followed by a 4-week open-label induction phase where they received esketamine 56 mg or 84 mg (flexible dose) twice weekly plus oral AD daily. There was then a 12-week optimisation phase where the frequency of treatment sessions was individualized from twice weekly to weekly or every other week. Finally, in the double-blind maintenance phase, patients in stable remission (n=176) or stable response (n=121) were randomised to continue with esketamine 56 mg or 84 mg or stop esketamine and switch to placebo once weekly or every 2 weeks (randomised withdrawal).

The primary endpoint for study TRD3003 was time from randomisation to first documentation of a relapse during the maintenance phase for subjects in stable remission at the end of the optimisation phase after 16 weeks of treatment with esketamine and oral AD. Relapse was defined as MADRS total score ≥22 for 2 consecutive assessments separated by 5-15 days and/or hospitalisation for worsening depression or any clinically relevant event determined per clinical judgement.

The baseline demographics of the stable remitters randomised to the maintenance phase were similar between the esketamine and placebo arms. The median subject age was 48 years, 66% were female, 90% Caucasian and the mean duration of the current episode of depression was 111 weeks. At the time of screening, 88.5% of patients had non-response to ≥2 oral ADs, with the remainder having prospective confirmation of non-response to a second oral antidepressant prior to initiating the induction phase.

Among patients in stable remission who entered the maintenance phase, 24 (26.7%) subjects in the esketamine group and 39 (45.3%) subjects in the placebo group experienced a relapse event, and the difference in terms of time to first relapse was statistically significant (HR=0.49; 95% CI 0.29, 0.84; p=0.003), demonstrating that the efficacy of esketamine at optimised doses is maintained following 4 weeks of induction treatment.

Kaplan-Meier curves of Time to Relapse in the Maintenance Phase (Study TRD3003; Full (Stable Remitters) Analysis Set)



In stable responders, 16 (25.8%) subjects in the esketamine group and 34 (57.6%) subjects in the placebo group experienced a relapse event and the difference in the time to relapse was statistically significant (HR=0.30; 95% CI 0.16, 0.55; p<0.001). For other secondary endpoints, numerical improvements were demonstrated in the esketamine arm relative to placebo. In stable remitters and stable responders, the remission rates were 65.2% vs 41.9% (stable remitters) and 46.8% vs 25.4% (stable responders) respectively. The response rates were 75.3% vs 55.8% (stable remitters) and 66.1% vs 33.9% (stable responders).

Overall, the clinical efficacy of esketamine in conjunction with an oral AD in the treatment of TRD was primarily demonstrated in study TRD3002, which supported the proposed flexible dosing of esketamine of up to 84 mg according to clinical response, and in study TRD3003 which demonstrated the efficacy of maintenance treatment of esketamine given once weekly or every 2 weeks. Although statistical significance for the primary endpoints was not met in studies TRD3001 and TRD3005, a clinically meaningful reduction from baseline of at least 2 points relative to placebo in the MADRS score was observed, which was consistent with the treatment effect seen in study TRD3002 at the end of 4 weeks. Improvements in secondary endpoints, including onset of response at Day 2, response rate, remission rate and patient-reported outcomes (SDS and PH-9) consistently favoured the esketamine arm in all 3 short-term studies.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of esketamine was based on 1708 patients with TRD in Phase II and III studies (1601 subjects in Phase III studies), with a combined cumulative exposure of 611 patient-years (601 patient-years in Phase III studies), and the combined exposure to placebo

was 108 patient-years (107 patient-years in Phase III studies). 479 subjects were exposed to esketamine for at least 6 months, and 178 were exposed for at least 12 months.

Overview of safety profile in adults (pooled studies TRD3001 and TRD3002, double-blind induction phase)

AE n (%)	ESK 56mg + oral AD (n=115)	ESK 84mg + oral AD (n=116)	Flex-dose ESK (n=115)	Total ESK (n=346)	Placebo + oral AD (n=222)
Any TEAE	100 (87%)	103 (88.8%)	98 (85.2%)	301 (87.0%)	143 (64.4%)
Treatment (intranasal)-related TEAE	89 (77.4%)	92 (79.3%)	90 (78/3%)	271 (78.3%)	93 (41.9%)
SAE	2 (1.7%)	0	1 (0.9%)	3 (0.9%)	1 (0.5%)
Treatment (intranasal)-related SAE	2 (0.6%)	0	0	0	0
Discontinuations of intranasal drug due to TEAE	1 (0.9%)	7 (6.0%)	8 (7.0%)	16 (4.6%)	3 (1.4%)
TEAE leading to death	0	0	1(0.9%)	1 (0.3%)	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overview of safety profile in elderly population (TRD3005, double-blind induction phase)

AE n (%)	ESK + oral AD (n=72)	Placebo+ oral AD (n=65)
Any TEAE	51 (70.8%)	39 (60%)
Treatment (intranasal)-related TEAE	42 (58.3%)	22 (33.8%)
SAE	3 (4.2%)	2 (3.1%)
Treatment (intranasal)-related SAE	2 (2.8%)	1 (1.5%)
Discontinuations of intranasal drug due to TEAE	4 (5.6%)	2 (3.1%)
TEAE leading to death	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overview of TEAEs in relapse prevention study (TRD3003)

	Induction phase	Optimisation phase	Maintenance Phase	
	ESK + oral AD (n=437)	ESK + oral AD (n=455)	ESK + oral AD (n=152)	Placebo + oral AD (N=145)
Any TEAE	336 (76.9%)	335 (73.6%)	125 (82.2%)	66 (45.5%)
Treatment (intranasal)-related TEAE	301 (68.9%)	281 (61.8%)	106 (69.7%)	37 (25.5%)
SAE	13 (3.0%)	11 (2.4%)	4 (2.6%)	1 (0.7%)
Treatment (intranasal)-related SAE	6 (1.4%)	0	0	0
Discontinuations of intranasal drug due to TEAE	22 (5.0%)	5 (1.1%)	4 (2.6%)	3 (2.1%)
TEAE leading to death	0	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

The most commonly reported treatment-emergent adverse events (AEs) and their incidences (esketamine vs placebo) in the pooled Phase III studies (TRD3001/3002) were nausea (28.3% vs 8.6%), dissociation (26.6% vs 3.6%), dizziness (23.7% vs 6.8%), vertigo (22.5% vs 2.3%), headache (20.2% vs 17.1%), dysgeusia (18.8% vs 13.5%), somnolence (17.3% vs 9.0%),

paraesthesia (12.4% vs 1.8%), hypoaesthesia (11.0% vs 1.4%) and hypoaesthesia oral (10.7% vs 1.4%). Most AEs were mild or moderate in severity, and the majority of post-dose AEs, such as dissociation and nausea, resolved within the same day. The types and incidence of these AEs in elderly subjects were generally consistent with the adult population. The safety profile in the short-term studies was also consistent with that observed in the long-term studies up to 1 year of exposure.

The incidence of serious AEs (SAEs) between esketamine and placebo was 0.9% vs 0.5% in the pooled TRD3001/3002 studies, 2.6% vs 0.7% in the maintenance phase of study TRD3003 and 4.2% vs 3.1% in study TRD3005. SAEs in the esketamine group related to study treatment included depression, headache, BP increased, suicidal ideation, sedation and anxiety disorder. The incidence of AEs leading to discontinuation in the Phase 3 studies was approximately 5-6% in the esketamine arm compared to 1.4-3.1% in placebo. AEs leading to discontinuation include anxiety, depression, BP increased, dizziness, suicidal ideation, headache and sedation.

There were 5 deaths reported in esketamine-treated subjects compared to none in subjects who received placebo (4/1708 in the Phase 2/3 studies and 1/1093 in an ongoing extension study TRD3008). AEs leading to death include completed suicide, road accident and acute cardiac and respiratory failure. None of these events were considered treatment-related. The overall rate of death in the completed Phase 2 and 3 studies (0.2%) was consistent with the background rate of death in MDD populations.

In the pooled safety population of all double-blind studies, TRD3001/3002/3005, the rates of worsening suicidal ideation/suicidal behaviour (SI/SB) and suicidality-related events between esketamine and placebo were comparable (8.3% vs 10.1% and 1.1% vs 0.8%, respectively). The incidence of completed suicides and suicide attempts reported for esketamine during the long-term open-label safety studies were comparable to the background rates in patients with TRD. The majority of events were reported in patients who had predisposed underlying disease. In view of the potential inherent risk in this vulnerable patient population, a warning statement on the risk of suicidality-events has been included in the package insert.

Other notable safety concerns with esketamine were dissociation, sedation and increased blood pressure (BP). Dissociative/perceptual changes (including distortion of time and space and illusions), derealisation and depersonalisation were the most common psychological effects of esketamine. These AEs were reported as transient and self-limiting, occurred on the day of dosing and the median duration did not exceed 2 hours. Severe dissociative AEs were reported in 3.8% of esketamine-treated subjects vs <1% in the placebo arm in the pooled dataset from the short-term studies, TRD3001/3002. There were no reports of severe dissociative AEs in elderly subjects in study TRD3005.

Sedation AEs were higher in subjects treated with esketamine than in subjects in the placebo group (5.5% vs 0.9% in the pooled dataset from study TRD3001/3002), and none were reported in either arm in study TRD3005. Sedative effects typically showed an onset at around 15 minutes after the first dose was administered, with symptoms peaking at 30 to 45 minutes post-dose and resolving by 1 to 1.5 hours post-dose. Rare cases (<1%) of deep, delayed or prolonged sedation have been reported, which might put patients at risk of accidents if they engage in hazardous activities without post-dose supervision.

Rates of AEs related to increased BP were higher in subjects treated with esketamine than in subjects in the placebo group (10.1% vs. 2.7% in the pooled dataset from study TRD3001/3002 and 13.9% vs. 6.2% in study TRD3005). The rates of acute hypertension were higher in the

esketamine arm vs placebo (<5% vs 0.9% in the pooled studies TRD3001/3002 and 11.1% vs 6.2% in study TRD3005).

Potentially serious, albeit transient AEs may occur after esketamine administration. These include acute hypertension, severe dissociative AEs and rare cases of deep, delayed or prolonged sedation. In view of these risks, healthcare professionals are advised to monitor patients on-site during and after each treatment session of esketamine until they are clinically stable. The implementation of physician education materials and a 'readiness-to-leave' checklist may mitigate this risk by reinforcing the need for post-dose monitoring. A patient guide has been implemented to inform patients of the risks of esketamine treatment. In addition, these AEs have also been included in the warnings and precautions section of the package insert.

Overall, esketamine presented an acceptable safety profile for the target patient population. The identified safety risks have been highlighted in the package insert and reinforced through the implementation of risk minimisation measures.

E ASSESSMENT OF BENEFIT-RISK PROFILE

TRD is a major contributing factor to the morbidity and mortality associated with depression. Patients with TRD are more likely to have lower remission rates, pronounced functional impairment, a substantially lower quality of life, and higher suicide rates compared to patients with MDD who respond to oral AD treatment. TRD in the elderly population is more severe and treatment is challenging given comorbid medical conditions. Current options include electroconvulsive shock therapy and deep brain stimulation, which may not be suitable for some patients.

The efficacy of esketamine nasal spray in combination with an oral AD was demonstrated in the short-term flexible dose study TRD3002, where a statistically significant reduction from baseline in MADRS score vs placebo and oral AD was shown after 4 weeks. This was supported by clinically meaningful improvements of at least 2 points in the MADRS score vs placebo in studies TRD3002 and TRD3005. Maintenance of efficacy was demonstrated in the relapse prevention study TRD3003, where patients in stable remission administered esketamine and oral AD demonstrated a significantly longer time to relapse compared to those who were switched to placebo and oral AD.

In addition, esketamine resulted in improvements in the MADRS score within 2 days after dosing. This fast onset may be an advantage in a setting where treatment of other ADs has been inadequate and there is a significant risk of suicidality.

In elderly subjects, a starting dose of 28 mg in study TRD3005 was considered appropriate for tolerability reasons. Despite the initial lower dose, similar numerical improvements in the MADRS score were observed compared to the adult patients in TRD3001 and TRD3002 at the end of 4 weeks following gradual dose titration. Furthermore, the safety profile in elderly patients was shown to be comparable to the adult population.

The safety profile of esketamine in combination with an oral AD was considered acceptable relative to the benefits. Most AEs were transient and resolved within a day following esketamine dosing. Notable safety concerns such as suicidality risk, dissociation, sedation and increased BP have been addressed in the package insert. Physician education materials and

a ‘readiness-to-leave’ checklist have been implemented to ensure that the drug is to be administered with post-dose monitoring under supervision of a healthcare professional until the patient is clinically stable. A patient guide has also been implemented to inform patients of the risks of esketamine treatment.

Overall, the benefit-risk profile of esketamine, in combination with an oral AD, for the treatment of TRD, is considered favourable.

F CONCLUSION

Based on the efficacy and safety data presented, the benefit-risk balance of Spravato for the treatment of TRD was deemed favourable and approval of the product registration was granted on 27 Oct 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

PRODUCT NAME

SPRAVATO® (esketamine) nasal spray 28mg/vial.

DOSAGE FORMS AND STRENGTHS

Nasal spray.

Clear, colorless, aqueous solution.

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 excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

SPRAVATO®, in combination with an oral antidepressant (SSRI or SNRI), 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).

Dosage and Administration

A treatment session consists of nasal administration of SPRAVATO® and post-administration observation under the supervision of a healthcare professional.

SPRAVATO® is for nasal use only. The nasal spray device is a single-use device that delivers a total of 28mg 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 28mg dose), 2 devices (for a 56mg dose) or 3 devices (for an 84mg dose), with a 5-minute rest between use of each device.

Blood pressure assessment before and after treatment

Assess blood pressure prior to dosing with SPRAVATO® (see *Warnings and Precautions*).

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 in patients with TRD (see *Warnings and Precautions*). Do not administer SPRAVATO® if an increase in blood pressure or intracranial pressure poses a serious risk (see *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 *Warnings and Precautions*).

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 *Adverse Reactions, Gastrointestinal Effects*).

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®.

For instructions to prepare the patient and for use of the nasal spray device, see *Instructions for Use and Handling*.

Dosage – Adults

The dosage recommendations for SPRAVATO® 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®

Induction Phase		Maintenance Phase
Weeks 1-4 (two treatment sessions/week):		**Weeks 5-8**:
Starting Day 1 dose*:	56 mg	56 mg or 84 mg once weekly
Subsequent doses:	56 mg or 84 mg	**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 reexamine the need for continued treatment.

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

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

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

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. Rare cases of deep, delayed or prolonged sedation have been reported. Sedation typically showed an onset at around 15 minutes after dosing, with symptoms peaking at 30 to 45 minutes post-dose and resolving by 1.5 hours post-dose. 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 *Warnings and Precautions – Effect on Blood Pressure, Potential for Cognitive and Motor Impairment and Effect on Driving*).

Missed treatment session(s)

In case one or two treatment sessions are missed, schedule the next session when the next dosage session was scheduled to occur based on current treatment frequency. If more than 2

treatment sessions have been missed, per clinical judgment, adjustment of the dose or frequency of SPRAVATO® may be clinically appropriate.

Special populations

Pediatrics (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. Use with caution in SPRAVATO®-treated patients with moderate hepatic impairment who may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO® has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended. (See *Pharmacokinetic Properties – Special populations, Hepatic impairment*).

Contraindications

SPRAVATO® is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see *Warnings and Precautions – Effect on blood pressure*):

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

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

Warnings and Precautions

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 *Adverse Reactions*). Patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing SPRAVATO® and treatment initiated only if the benefit outweighs the risk (see *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.
- Hemodynamically 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 etiology.

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 and 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.

Closely monitor blood pressure with concomitant use of SPRAVATO® with psychostimulants or monoamine oxidase inhibitors (MAOIs) (see *Interactions*).

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 *Adverse Reactions*). 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 by a healthcare professional to assess when the patient is considered clinically stable (see *Dosage and Administration/Post-administration observation*).

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, 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 *Clinical Studies – Effects on Driving*). 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 *Warnings and Precautions, Potential for Cognitive and Motor Impairment*).

Urinary Tract Symptoms

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 a year (see *Clinical Studies*).

Urinary tract and bladder symptoms have been reported with SPRAVATO® use. It is recommended to monitor for urinary tract and bladder symptoms during the course of treatment.

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 minimized due to the product's design and the administration taking place under the supervision of 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.

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 brady- or tachyarrhythmias that lead to hemodynamic instability.
- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

Suicide/suicidal thoughts or clinical worsening

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.

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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

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, modafanil, 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.

Pharmacokinetic interactions

Esketamine is extensively metabolized 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 *Pharmacokinetic Properties*).

Effect of other drugs on esketamine

Hepatic enzyme inhibitors

Pretreatment 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 pretreatment.

Pretreatment 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 pretreatment.

Hepatic enzyme inducers

Pretreatment 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. Pretreatment 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.

Pretreatment 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 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.

Pregnancy and Breast-feeding

Pregnancy

SPRAVATO® is not recommended 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 fetuses cannot be excluded. To avoid exposing the fetus 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 counseled about the potential risk to the fetus and clinical/therapeutic options as soon as possible.

Ketamine, the racemic mixture of arketamine and esketamine, administered intravenously at high anesthetic dose levels to female rats in the second trimester of pregnancy caused neuronal cell abnormalities in the brains of their offspring which showed behavioral changes and impaired memory up to young adult age. When female monkeys were treated intravenously with ketamine at high anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. 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-fetal developmental toxicity studies in rats and rabbits, nasally-administered ketamine did not induce adverse findings in the offspring other than a reduction in fetal body weight in rabbits. It cannot be excluded that esketamine induces neurotoxicity in developing fetuses (see *Non-Clinical Information*).

Breast-feeding

SPRAVATO® is not recommended 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 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. (See *Non-Clinical Information*)

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 *Adverse Reactions*). 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 *Warnings and Precautions and Clinical Studies*).

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that have been considered to be reasonably associated with the use of esketamine based on the comprehensive assessment of the available adverse event information. A causal relationship with esketamine cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Adverse Reactions from Clinical Studies in Treatment-Resistant Depression (TRD)

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) treatments, 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.

Adverse Events Reported as Reasons for Discontinuation of Treatment

In short-term studies in both adult (pooled TRD3001/TRD3002) and elderly (TRD3005) patients, the proportion of patients that received SPRAVATO® plus oral AD and discontinued treatment because of an adverse event was 4.6% for adult and 5.6% for elderly patients, respectively, compared to 1.4% for adult and 3.1% for elderly patients receiving oral AD plus placebo nasal spray. In a long-term study, the discontinuation rates because of an adverse event were similar for patients receiving SPRAVATO® plus oral AD and oral AD plus placebo nasal spray, 2.6% and 2.1%, respectively. Across all Phase 3 studies, adverse events leading to SPRAVATO® discontinuation in more than 2 patients (>0.1%) were (in order of frequency): anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack and sedation.

Common Adverse Reactions

The most commonly observed adverse reactions in TRD patients treated with SPRAVATO® plus oral AD (incidence ≥10% and greater than oral AD plus placebo nasal spray) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, blood pressure increased, anxiety 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.

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

	Double-Blind Population		Open-Label Population	
	SPRAVATO® + Oral AD (N=587)	**Oral AD + Placebo nasal spray (N=486)**	**SPRAVATO® + Oral AD (N=1335)**	**All SPRAVATO® Population (N=1709)**
Psychiatric disorders				
Dissociation†	221 (37.6%)	30 (6.2%)	511 (38.3%)	690 (40.4%)
Anxiety†	63 (10.7%)	28 (5.8%)	155 (11.6%)	220 (12.9%)
Euphoric mood	20 (3.4%)	3 (0.6%)	51 (3.8%)	73 (4.3%)
Nervous system disorders				
Dizziness†	175 (29.8%)	33 (6.8%)	490 (36.7%)	628 (36.7%)
Sedation†	124 (21.1%)	35 (7.2%)	321 (24.0%)	434 (25.4%)
Headache†	115 (19.6%)	60 (12.3%)	293 (21.9%)	410 (24.0%)
Dysgeusia†	113 (19.3%)	54 (11.1%)	207 (15.5%)	293 (17.1%)
Hypoesthesia†	103 (17.5%)	7 (1.4%)	204 (15.3%)	285 (16.7%)
Lethargy†	47 (8.0%)	21 (4.3%)	95 (7.1%)	148 (8.7%)
Dysarthria†	18 (3.1%)	1 (0.2%)	37 (2.8%)	56 (3.3%)
Mental impairment	14 (2.4%)	4 (0.8%)	26 (1.9%)	41 (2.4%)
Tremor†	13 (2.2%)	2 (0.4%)	27 (2.0%)	45 (2.6%)
Ear and labyrinth disorders				
Vertigo†	115 (19.6%)	16 (3.3%)	211 (15.8%)	303 (17.7%)
Cardiac disorders				
Tachycardia†	6 (1.0%)	2 (0.4%)	19 (1.4%)	27 (1.6%)
Respiratory, thoracic and mediastinal disorders				
Nasal discomfort†	43 (7.3%)	21 (4.3%)	96 (7.2%)	133 (7.8%)
Gastrointestinal disorders				
Nausea	144 (24.5%)	28 (5.8%)	321 (24.0%)	458 (26.8%)
Vomiting	49 (8.3%)	6 (1.2%)	123 (9.2%)	177 (10.4%)
Dry mouth	23 (3.9%)	8 (1.6%)	42 (3.1%)	68 (4.0%)
Salivary hypersecretion	5 (0.9%)	1 (0.2%)	5 (0.4%)	9 (0.5%)

Skin and subcutaneous tissue disorders				
Hyperhidrosis	21 (3.6%)	5 (1.0%)	52 (3.9%)	77 (4.5%)
Renal and urinary disorders				
Pollakiuria†	13 (2.2%)	2 (0.4%)	26 (1.9%)	40 (2.3%)
General disorders and administration site conditions				
Feeling abnormal	24 (4.1%)	3 (0.6%)	53 (4.0%)	72 (4.2%)
Feeling drunk	23 (3.9%)	1 (0.2%)	31 (2.3%)	51 (3.0%)
Investigations				
Blood pressure increased†	68 (11.6%)	19 (3.9%)	165 (12.4%)	220 (12.9%)

* Note: The following studies are included in the Double-Blind Population: TRD2003 (Double-Blind Phase), TRD3001, TRD3002, TRD3003 (Maintenance Phase), TRD3005. The following studies are included in the Open-Label Population: TRD2003 (Open-Label Phase), TRD3003 (Induction and Optimization 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.

† The following terms were combined:
Dissociation includes: dissociation; depersonalization/derealization disorder; derealization; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change.
Anxiety includes: anxiety; anticipatory anxiety; anxiety disorder; generalized anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor.
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.
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; extrasystole.
Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness; nasal pruritus
Pollakiuria includes: pollakiuria; micturition disorder.
Blood pressure increased includes: blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis.

Dissociation/perceptual changes

The most common psychological effects of esketamine have been dissociative/perceptual changes (including distortion of time and space and illusions), derealization and depersonalization. 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. Based on an objective scale of sedation, the Modified Observer's Alertness/Sedation scale (MOAA/s), the incidence of deep sedation (MOAA/s score <2) was 2.3% in patients treated with SPRAVATO® + oral antidepressant. Based on MOAA/s the incidences of late onset (more than 45 min post-dose) or prolonged (>1.5 hours post-dose) deep sedation were rare (<1%). 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 hemodynamic 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: 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: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled, Fixed-dose Study

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

Laboratory values

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

Overdose

No cases of overdose were reported in clinical studies with SPRAVATO®. The potential for overdose of SPRAVATO® by the patient is minimized due to the product's design and the administration taking place under the supervision of a healthcare professional (see *Dosage and Administration*).

Symptoms and signs

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, hypoesthesia, feeling abnormal, nausea and vomiting.

Treatment

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Management of SPRAVATO® overdose should consist of treating clinical symptoms and relevant monitoring. Close supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

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.

Putative etiological 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 behavior. 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 signaling 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, one study in adult subjects with major depressive disorder and one study in healthy subjects. On-road driving performance was assessed by the mean standard deviation of the lateral position (SDLP), a measure of driving impairment.

A single-blind, placebo-controlled study in 25 adult subjects with major depressive disorder evaluated the effects of a single 84-mg dose of esketamine nasal spray on next day driving. An ethanol-containing beverage was used as a positive control. The SDLP after administration of single 84-mg dose of esketamine nasal spray was similar to placebo. The upper limit of the two-sided 95% confidence interval (CI) of the mean difference between single-dose of esketamine and placebo was 0.58 cm, which is less than the pre-specified non-inferiority margin of 2.4 cm. The lower limit of the 95% CI of the mean difference between ethanol and placebo was 1.03 cm ($p<0.001$), verifying assay sensitivity.

A randomized, double-blind, cross-over, placebo-controlled study in 23 healthy subjects evaluated the effects of a single 84-mg dose of esketamine nasal spray on driving. Mirtazapine

was used as a positive control. Driving performance was assessed at 8 hours after esketamine or mirtazapine administration. The SDLP after esketamine nasal spray administration was similar to placebo. The upper limit of the two-sided 95% CI of the mean difference between esketamine and placebo was 0.86 cm, which is less than the pre-specified non-inferiority margin of 2.4 cm. The lower limit of the 95% CI of the mean difference between mirtazapine and placebo was 1.12 cm (p=0.001), verifying assay sensitivity. Of the 23 subjects evaluated, 21 subjects completed the test successfully. Two subjects discontinued the driving test after receiving esketamine because of a perceived inability to drive.

Effect on QT/QTc interval and cardiac electrophysiology

Treatment with SPRAVATO® did not prolong the QTc interval. The effect of SPRAVATO® (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. Maximum esketamine concentrations in plasma produced by the intravenous infusion were approximately 3-times higher than the maximum concentrations produced by the nasal dose of 84 mg. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval remained below 10 msec, at all evaluated time-points, based on Fridericia's correction method (QTcF) for both treatment groups.

Clinical studies

The efficacy and safety of SPRAVATO® nasal spray was evaluated in five Phase 3 clinical studies 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®.

Treatment-resistant depression – Short-term studies

SPRAVATO® was evaluated in three Phase 3 short-term (4-week) randomized, double-blind, multicenter, 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-Asberg 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 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 favoring SPRAVATO® plus newly initiated oral AD compared with standard of care (newly initiated oral AD) plus placebo nasal spray (Table 5 [MMRM]). 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 favored SPRAVATO® plus a newly initiated oral AD compared to standard of care (newly initiated oral AD) plus placebo nasal spray.

Table 5: Primary Efficacy Results for Change in MADRS Total Score for 4 Week Clinical Trials (MMRM)

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)	-18.8 (1.3)	-4.1 (-7.7, -0.5)[#]

TRD3002	SPRAVATO® 84 mg + oral AD	114	37.8 (5.6)	-18.5 (1.4)	-3.2 (-6.9, 0.5)[#]
	Oral AD + Placebo nasal spray	113	37.5 (6.2)	-14.8 (1.3)	-
	SPRAVATO® (56 mg or 84 mg) + oral AD	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3; -0.6)[‡]
	Oral AD + Placebo nasal spray	109	37.3 (5.7)	-15.8 (1.3)	-
TRD3005 (≥65 years)	SPRAVATO® (28 mg, 56 mg or 84 mg) + oral AD	72	35.5 (5.9)	-10.2 (1.5)	-3.6 (-7.2, 0.1)[#]
	Oral AD + Placebo nasal spray	65	34.8 (6.4)	-6.2 (1.5)	-

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

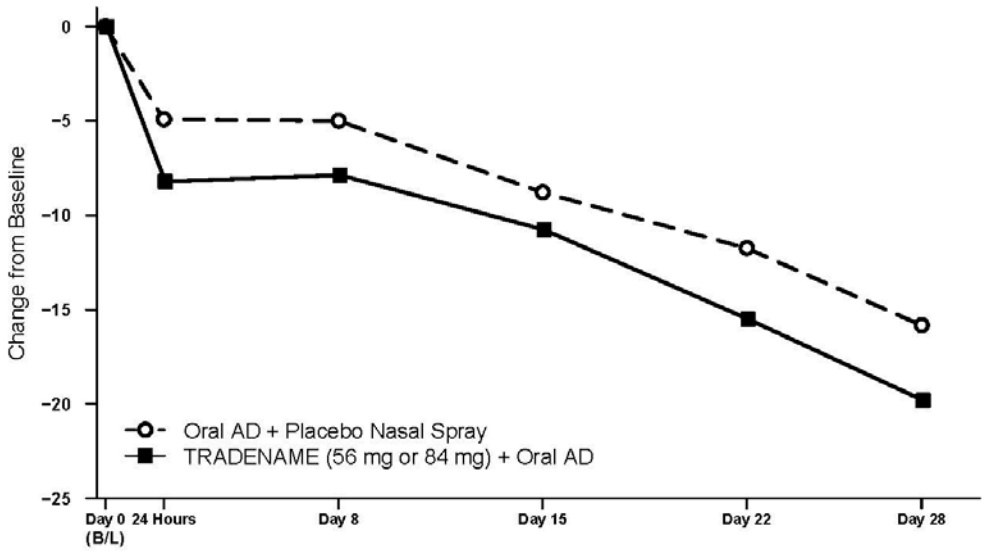
‡ Treatment groups that were statistically significantly superior to oral AD + placebo nasal spray

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 randomized to SPRAVATO® were on 84 mg. Figure 1 [MMRM Analysis] 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.

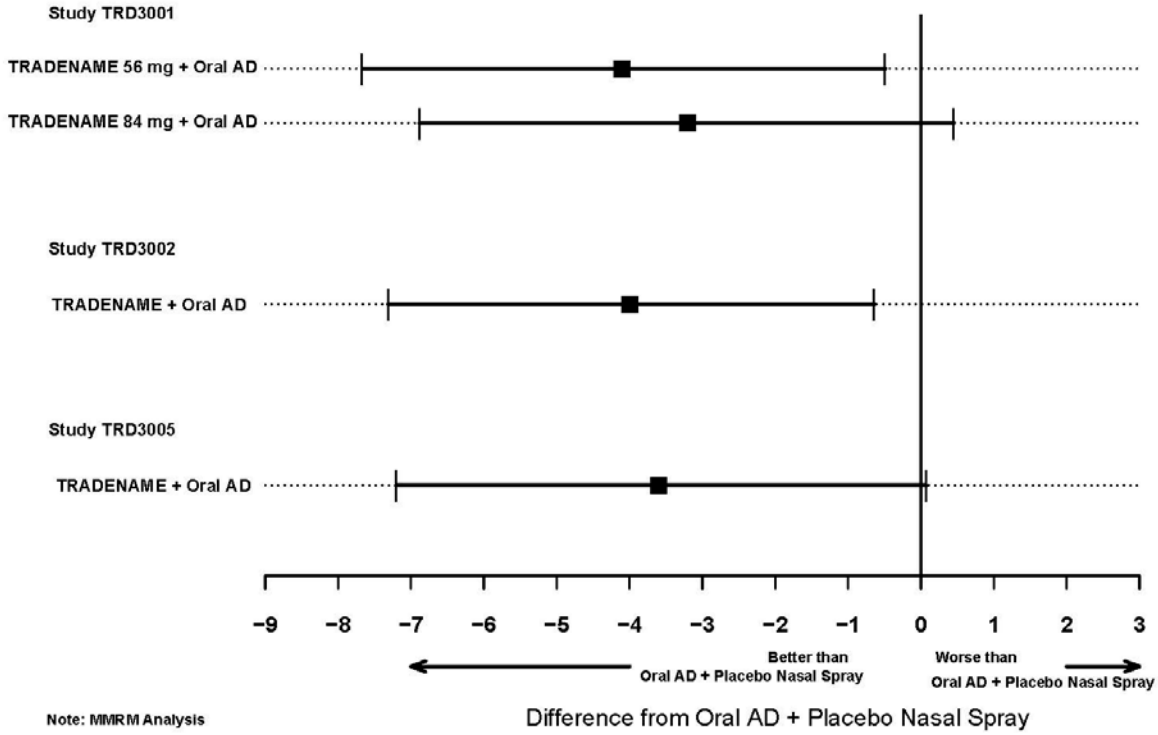
Figure 1: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Study TRD3002* (Full Analysis Set) – MMRM Analysis



* Note: In this flexible-dose study, dosing was individualized 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.

In addition, in TRD3002 study SPRAVATO® plus oral AD was superior to oral AD plus placebo nasal spray in terms of mean change from baseline in MADRS total score at the end of Week 4. A consistent treatment difference was observed in Studies TRD3001 and TRD3005. (Figure 2 [MMRM]).

Figure 2: Difference from SPRAVATO® Plus Oral AD vs. Oral AD Plus Placebo Nasal Spray in Mean Change from Baseline in MADRS Total Score at the End of Week 4 (MMRM)



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 6).

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 6).

Table 6: Response and Remission Rates in 4 Week Clinical Trials

		Number of Patients (%)					
		Response Rate[†]					Remission Rate[‡]
Study No.	Treatment Group[§]	24 hours	Week 1	Week 2	Week 3	Week 4	Week 4

	SPRAVATO® 56 mg + oral AD	20 (19.0%)	21 (18.4%)	29 (26.4%)	52 (48.6%)	60 (54.1%)	40 (36.0%)
TRD3001	SPRAVATO® 84 mg + oral AD	17 (16.3%)[#]	16 (15.0%)	25 (25.3%)	33 (34.4%)	52 (53.1%)	38 (38.8%)
	Oral AD + placebo nasal spray	8 (7.9%)	5 (4.5%)	15 (14.2%)	25 (23.8%)	42 (38.9%)	33 (30.6%)
TRD3002	SPRAVATO® 56 mg or 84 mg + oral AD	18 (16.5%)	15 (13.8%)	29 (27.1%)	54 (52.4%)	70 (69.3%)	53 (52.5%)
	Oral AD + placebo nasal spray	11 (10.8%)	13 (12.4%)	23 (22.5%)	35 (33.7%)	52 (52.0%)	31 (31.0%)
TRD3005 (≥65 years)	SPRAVATO® 28 mg, 56 mg or 84 mg + oral AD	NA	4 (6.1%)	4 (5.9%)	9 (15.0%)	17 (27.0%)	11 (17.5%)
	Oral AD + placebo nasal spray	NA	3 (4.8%)	8 (12.9%)	8 (14.3%)	8 (13.3%)	4 (6.7%)

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

Relapse-prevention study

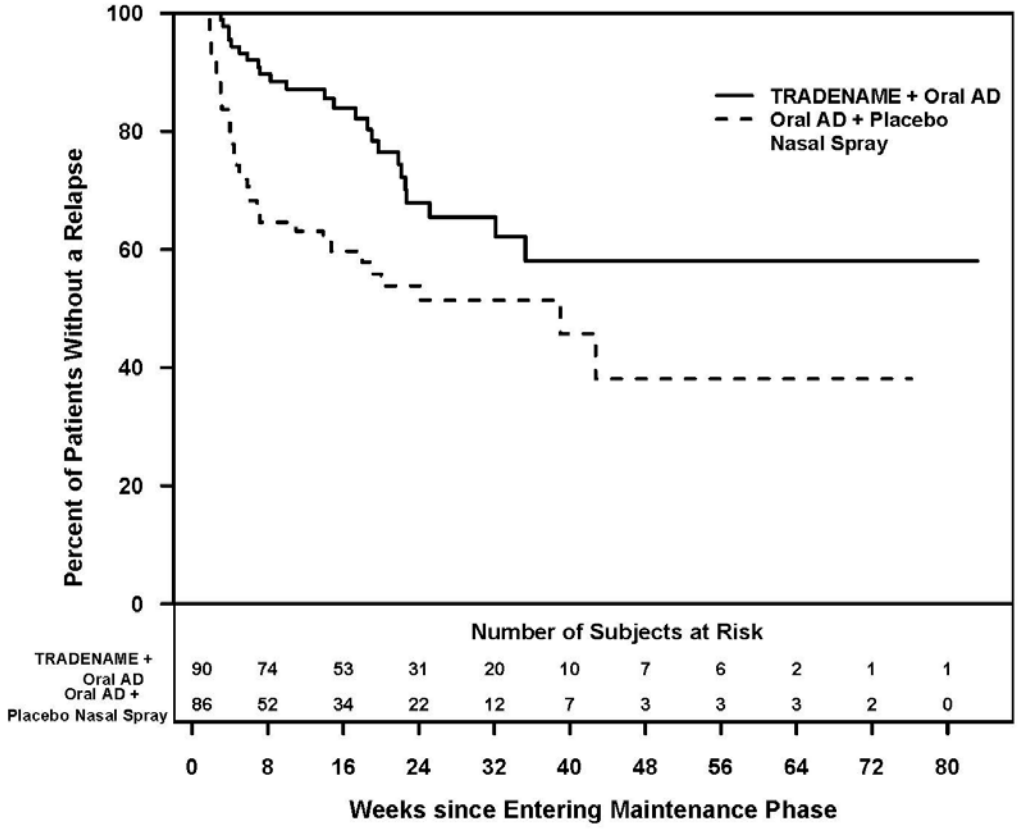
Study SUSTAIN-1 (TRD3003) was a long-term randomized, double-blind, parallel-group, active-controlled, multicenter, relapse prevention study. Overall a total of 705 patients were enrolled; 437 directly enrolled; 150 transferred from TRD3001, and 118 transferred from TRD3002. Patients directly enrolled 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 optimization 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 optimization phase, patients in stable remission or stable response were randomized 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 optimization phase and stable response was defined as ≥50% reduction in the MADRS total score from baseline for the last 2 weeks of the optimization phase, but not in stable remission.

The baseline demographic and disease characteristics of the patients randomized 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 3). Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalization 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 3: Time to Relapse in Patients in Stable Remission in Study TRD3003 (Full Analysis Set)



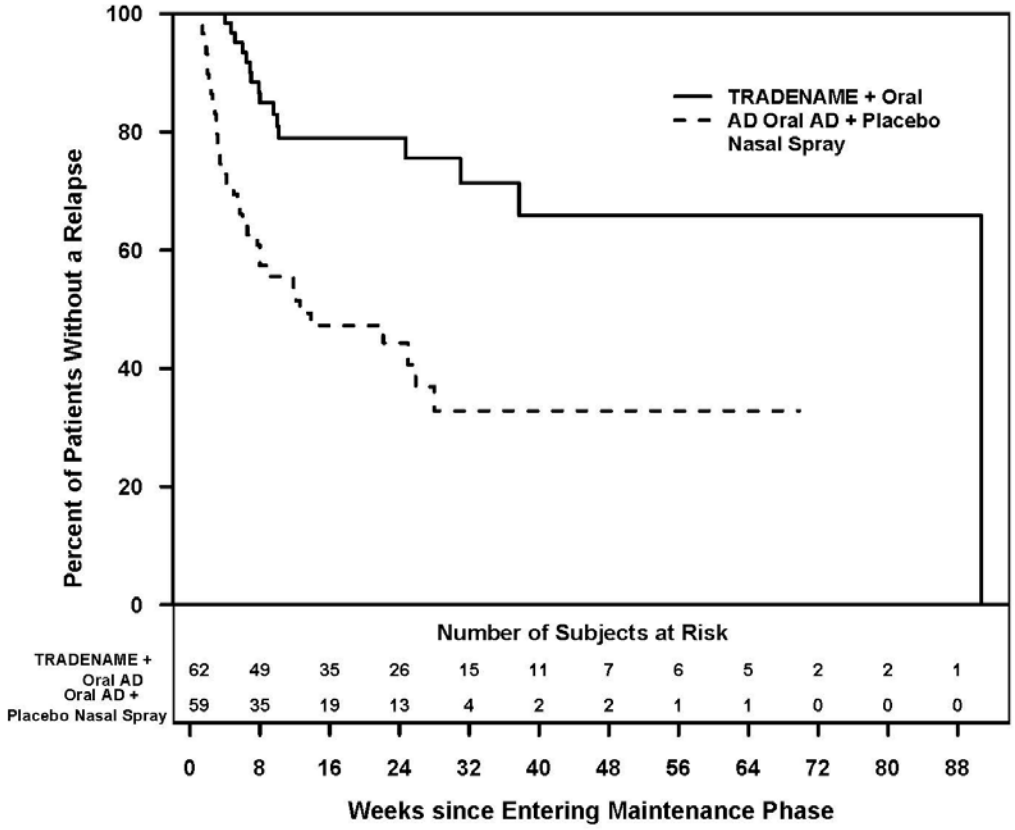
For patients in stable remission, the estimated hazard ratio (95% CI) of SPRAVATO® plus oral AD relative to standard of care (oral AD) plus placebo nasal spray based on weighted estimates was 0.49 (95% CI: 0.29, 0.84), indicating that, patients who were in stable remission and continued treatment with 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 4). 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 4: 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.

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

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 7. Of the patients randomized to SPRAVATO®, 60% received 84 mg and 40% received 56 mg dose.

Table 7: 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%)

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.

Dose-response study in treatment-resistant depression

A Phase 2 adjunctive, doubly-randomized, 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 8).

Table 8: 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

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 *Dosage and 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.

Metabolism

Esketamine is extensively metabolized 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 metabolized via CYP-dependent pathways to other metabolites, some of which undergo glucuronidation.

Excretion

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 feces, respectively. Following oral administration of radiolabelled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and feces, 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 [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.

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.

NON-CLINICAL INFORMATION

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 anesthetic 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.

Carcinogenicity and Mutagenicity

Once-daily nasal administration of esketamine did not increase the incidence of tumors 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.

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.

Reproductive Toxicity

In an embryo-fetal 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 100 mg/kg/day. The high dose was lowered from 100 to 50 mg/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 fetuses cannot be excluded. (see *Pregnancy and Breast-feeding*).

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.

PHARMACEUTICAL INFORMATION

List of Excipients

Citric acid monohydrate
Edetate disodium
Sodium hydroxide
Water for injection

Incompatibilities

Not applicable.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

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

Nature and Contents of Container

SPRAVATO® is a drug-device combination product, which is assembled in a filled Type 1 glass vial containing esketamine drug product solution with rubber stopper into a single-use nasal spray device. The device is ready to use once removed from its secondary packaging.

SPRAVATO® is available in packs of 1, 2 or 3 devices. Not all pack sizes may be marketed.

PRODUCT REGISTRANT

Johnson & Johnson Pte Ltd
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

BATCH RELEASERS

Janssen Cilag Manufacturing LLC
State Road 993, KM 0.1,
Mamey Ward, Gurabo,
Puerto Rico (PR), 00778,
United States (USA)

DATE OF REVISION OF TEXT

05 October 2020 (CCDS 10 July 2019)

Instructions for Use and Handling and Disposal

SPRAVATO®

(esketamine)

Nasal Spray Device

28 mg per device

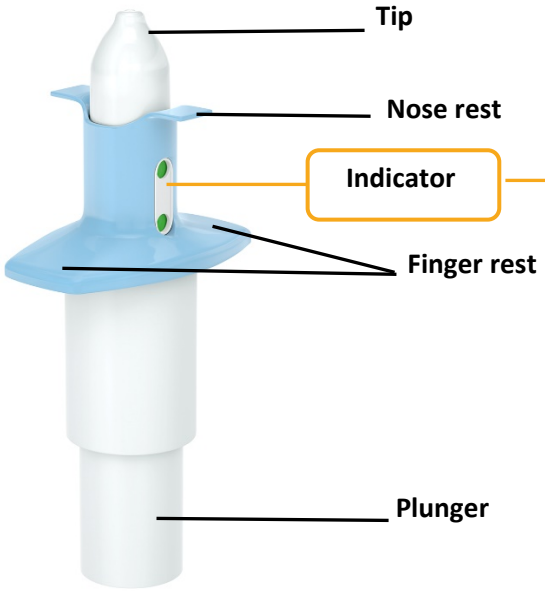
Important

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.

Need help?

Ask your doctor about any questions you may have. For additional assistance or to share your feedback, refer to the Package Leaflet for your local representative contact information.

Nasal Spray Device



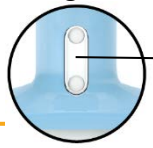
Indicator

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

2 green dots (0 mg delivered)

1 green dot

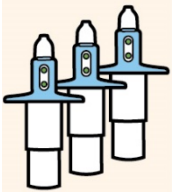
No green dots (28 mg delivered)



Step 1 Get ready

Before first device only:

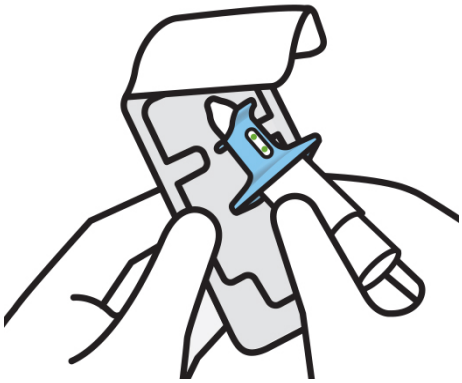
Instruct patient to blow nose **before first device only**.



Confirm required number of devices.

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

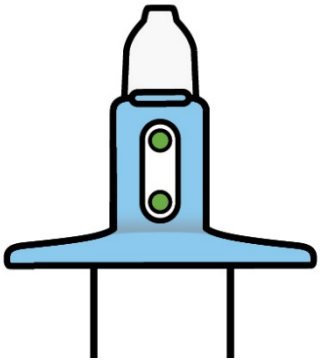
Step 2 Prepare device



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.

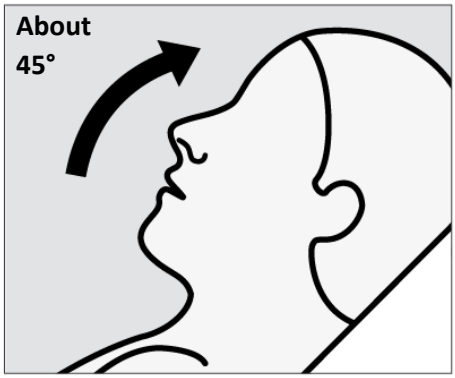
Hand device to patient.

Step 3 Prepare patient

Patient should:

Hold device as shown with the thumb gently supporting the plunger.

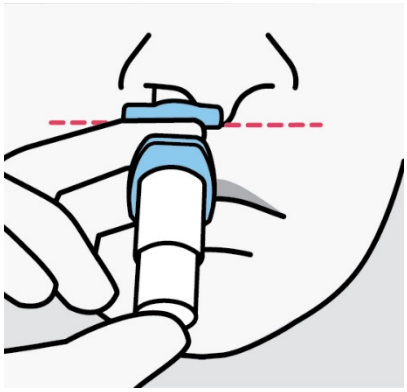
Do not press the plunger.



Patient should:

Recline head at about **45 degrees** during administration to keep medication inside the nose.

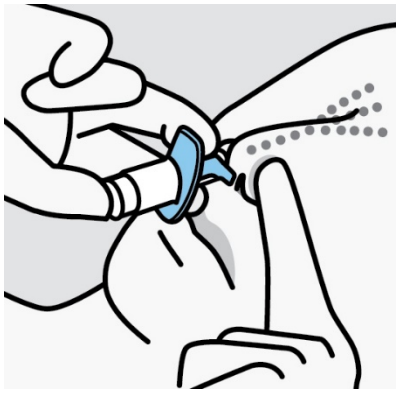
Step 4 Patient sprays once into each nostril



Patient should:

Insert tip straight into the **first nostril**.

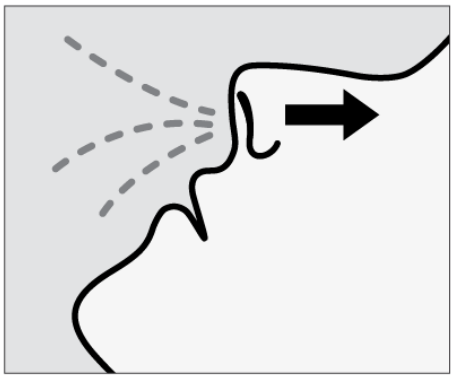
Nose rest should touch the **skin between the nostrils**.



Patient should:

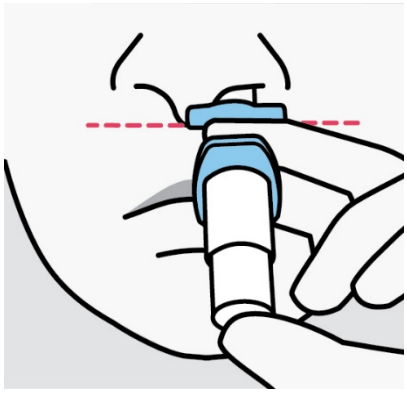
Close opposite nostril.

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.

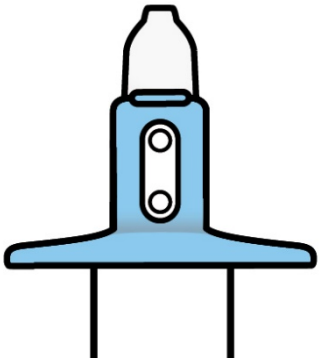


Patient should:

Switch hands to insert tip into the **second nostril**.

Repeat Step 4 to deliver second spray.

Step 5 Confirm delivery and rest

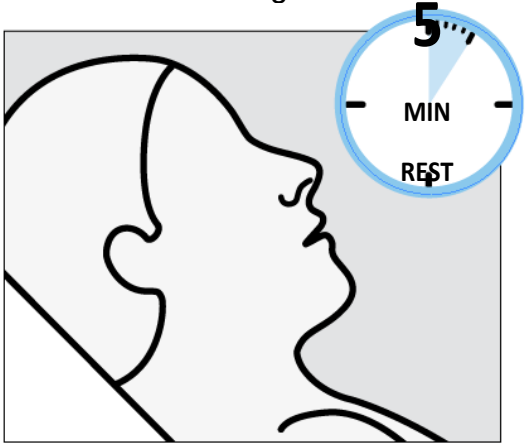


Healthcare professional:

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.



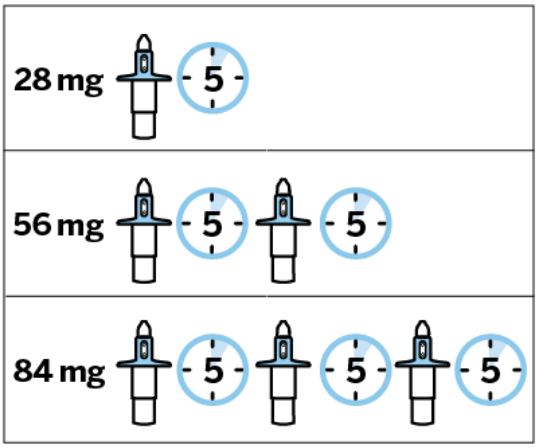
Patient should:

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.

IMPORTANT: Ensure that patient **waits 5 minutes after each device** to allow medication to absorb.

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

IFU issued date: 27 September 2018