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Long-Term Safety and Efficacy of Esketamine in Patients With Treatment-Resistant Depression: A Review of Interim Results From the SUSTAIN-3 Trial

KEY TAKEAWAYS

- Treatment-resistant depression (TRD) is associated with a high level of clinical, economic, and social burden for patients, caregivers, and society.^{1,2}
- In the STAR*D study, remission in the third round of oral antidepressants (OADs) alone occurred in approximately 14% of patients with TRD.³
- In an interim analysis of SUSTAIN-3 trial (NCT02782104) data, open-label treatment with esketamine nasal spray plus an OAD in patients with TRD aged 18 to 64 years was associated with safety and efficacy results consistent with those seen in the short-term esketamine TRD trials.⁴⁻¹²

INDICATIONS:

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

LIMITATIONS OF USE:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.
- SPRAVATO® is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO® as an anesthetic agent have not been established.

IMPORTANT SAFETY INFORMATION

WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).**
- **Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO® prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).**
- **SPRAVATO® is only available through a restricted program called the SPRAVATO® REMS (5.4).**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO® is not approved for use in pediatric patients (5.5).**

Please see additional Important Safety Information throughout and full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#) for SPRAVATO®.

INTRODUCTION

In the STAR*D study of adults with major depressive disorder (MDD) (N = 4041), approximately 1 in 3 individuals did not respond to an oral antidepressant (OAD) alone.³ Those who have an inadequate response to at least 2 different antidepressants given at an adequate dose and for an appropriate duration in the current depressive episode are commonly characterized as having treatment-resistant depression (TRD).¹³ In the STAR*D study, remission in the third round of OADs alone occurred in approximately 14% of patients with TRD.³

The ongoing SUSTAIN-3 trial (NCT02782104) investigates the long-term safety and efficacy of individualized, intermittently dosed esketamine nasal spray used with an OAD in patients with TRD.^{14,15} This clinical brief reviews both the established short-term efficacy and safety profile of esketamine nasal spray and the study design and interim analysis results of the SUSTAIN-3 study.

BURDEN OF ILLNESS IN TRD

TRD is associated with high levels of clinical, economic, and humanistic burden. In a meta-analysis of 62 articles related to TRD that were published from 1996 to 2013, several comorbidities were reported more commonly in patients with TRD than in those with treatment-responsive depression. Cardiovascular disease was reported in 56% of 2598 patients with TRD in 1 study vs a mean (SD) of 49% (9%) of 3702 (666) patients with treatment-responsive depression in 2 studies. Malaise/fatigue was noted in 52% of 2412 patients with TRD in 1 study vs 44% of 3311 patients with treatment-responsive depression in 1 study.¹

Results of the same analysis indicated that per-patient total annual costs (2012 US\$; direct and indirect) were about twice as high for patients with TRD as they were for age-matched patients with

treatment-responsive depression (\$20,120 vs \$10,592).¹ In an analysis of OptumHealth Care Solutions US prescription claims data from 2009 to 2015, patients with MDD who initiated a third antidepressant or augmentation medication were identified as having TRD (n = 6411).¹⁶ For these patients, all-cause pharmacy and medical costs increased with the number of lines of therapy of adequate dose and duration; from TRD start to up to 2 years later, mean annual cost per patient (2015 US\$) was \$12,047 for 2 lines of therapy (n = 438) and \$18,667 for 6 or more lines of therapy (n = 2656).¹⁶ As the number of lines of therapy increased, costs related to mental health and depression also increased.¹⁶

TRD is also associated with productivity costs. A model of TRD-related economic burden in the United States input productivity and unemployment costs from Medicare, Medicaid, commercial plan, and US Veterans Health Administration payer types drawn from a 2017 Kantar National Health and Wellness Survey study.¹⁷ Using US Census Bureau–reported prevalence of payer type in the insured US population, the model weighted these costs and calculated that annual, per-patient productivity costs were \$6727 higher in adults with TRD than they were in patients with no MDD (2018 US\$).¹⁷

Finally, TRD has a substantial negative impact on caregiver quality of life, representing a considerable humanistic burden. Linear regression analyses for results of a population-based survey of caregivers (N = 1708) estimated that adjusted annual indirect costs (2018 US\$) were \$3360 higher for caregivers of patients with TRD than for caregivers who were assisting individuals with other diseases (\$11,120 vs \$7761, respectively); adjusted annual direct costs were \$9163 higher for caregivers of patients with TRD than for those caring for patients with other conditions (\$29,805 vs \$20,642; all $P \leq .0001$).² Caregivers of patients with TRD (n = 169) also screened positive for depression at higher rates than did other caregivers (n = 1070) (16.8% vs 6.7%; $P \leq .0001$).²

IMPORTANT SAFETY INFORMATION for SPRAVATO (esketamine) (CONTINUED) CONTRAINDICATIONS

SPRAVATO® is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
- History of intracerebral hemorrhage.
- Hypersensitivity to esketamine, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS

Sedation: In clinical trials, 48% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% to 0.4% of SPRAVATO®-treated patients experienced loss of consciousness.

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

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

Please see additional Important Safety Information throughout and full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

SPRAVATO® (ESKETAMINE) CIII NASAL SPRAY

Esketamine is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist. Esketamine nasal spray (SPRAVATO®; Janssen) given in combination with a newly initiated OAD is indicated for the treatment of TRD in adults and depressive symptoms in adults with MDD who have acute suicidal ideation or behavior.⁵ The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO. SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.⁵

SPRAVATO received FDA approval based on results of three 4-week studies (TRANSFORM-2 [NCT02418585], Aspire I [NCT03039192], Aspire II [NCT03097133]) and 1 longer-term phase 3 trial (SUSTAIN-1 [NCT02493868]). In these studies, clinically meaningful reductions in depressive symptoms, as measured by the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS), were observed.⁵⁻⁹

Efficacy and Safety of SPRAVATO in Short-Term and Maintenance-of-Effect Studies

The TRANSFORM-2 and SUSTAIN-1 randomized clinical trials compared outcomes of treatment with esketamine plus OAD to those of placebo plus OAD in adults (aged 18-64 years) with TRD (Table 1).^{5-7,10,11,18}

In TRANSFORM-2, for those treated with esketamine plus an OAD (n = 114) compared with those treated with OAD plus placebo nasal spray (n = 109), mean improvement in MADRS score after 28 days was significantly greater (difference of least square means [SE], -4.0 [1.69]; 95% CI, -7.31 to -0.64; P = .020).¹⁰ The least-squares mean (SE) change in MADRS total score from baseline to end of week 4 was -19.8

(1.3) in the esketamine arm versus -15.8 (1.3) in the placebo arm.⁵ A key hierarchical secondary end point evaluated the proportion of patients with a decrease in MADRS score of at least 50% at day 2 that was maintained to day 28. Although a higher proportion of patients achieved clinical response in the esketamine plus OAD-arm vs the placebo plus OAD-arm (7.9% vs 4.6%, respectively), the difference was not significant (P = .321). The remaining key secondary end points (change from baseline to day 28 in Sheehan Disability Scale [SDS] score and 9-item Patient Health Questionnaire [PHQ-9], respectively) could not be formally assessed.¹⁰

In SUSTAIN-1, compared with placebo plus OAD, treatment with esketamine plus OAD significantly reduced relapse risk during a treatment maintenance phase by 51% among the group that had achieved stable remission at the end of a 16-week induction/optimization phase (95% CI, 16%-71%; P = .003) (number needed to treat [NNT], 6) and by 70% among those who had achieved stable response at baseline (95% CI, 45%-84%; P < .001) (NNT, 4). Relapse was defined as a MADRS total score of at least 22 for 2 consecutive assessments 5 to 15 days apart; hospitalization for suicide attempt, suicide prevention, completed suicide, or worsening depression; or another event determined by an adjudication committee to be suggestive of relapse. Stable remission was defined as a MADRS score of 12 or less in at least 3 of the last 4 weeks of the optimization phase. Stable response was defined as a reduction in MADRS score from baseline by at least 50% in the last 2 weeks of the treatment optimization phase but without attaining remission. Median time to relapse, interquartile range, and 95% confidence intervals could not all be estimated for any group.¹¹

Safety of esketamine plus OAD treatment in adults with TRD (N = 1709) was assessed across 5 phase 3 studies (including TRANSFORM-2 and SUSTAIN-1) and 1 phase 2 dose-ranging study. The most common adverse events (AEs) were described (Table 2).⁵⁻⁷ In TRANSFORM-2, most treatment-emergent adverse events (TEAEs) (93.7%) occurred

IMPORTANT SAFETY INFORMATION (CONTINUED) WARNINGS AND PRECAUTIONS (CONTINUED)

Dissociation: The most common psychological effects of SPRAVATO® were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of SPRAVATO®-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO®; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Abuse and Misuse: SPRAVATO® contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.

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and resolved on the day of dosing. The majority of TEAEs were of mild or moderate severity.^{10,19} Across TRANSFORM-2 and another 4-week study, 4.6% of patients younger than 65 years treated with esketamine plus OAD discontinued treatment because of an AE vs 1.4% of patients in this age group treated with placebo plus OAD. In SUSTAIN-1, AE discontinuation rates were similar between groups (2.6% and 2.1% for patients receiving esketamine plus OAD and placebo plus OAD, respectively). Across the phase 3 studies, AEs leading to esketamine plus OAD treatment discontinuation in more than 2 patients were anxiety (1.2%), depression (0.9%), blood

pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%), and sedation (0.2%).⁵

SUSTAIN-3

SUSTAIN-3 is an ongoing, phase 3, open-label study of patients (aged ≥ 18 years) with treatment-resistant MDD who previously participated in 1 of 6 phase 3 parent studies of esketamine nasal spray

Table 1. Pivotal Short- and Long-Term Studies of Esketamine Nasal Spray in Patients With TRD^{5-7,10,11,18}

	TRANSFORM-2	SUSTAIN-1
Patient population	Adults (aged 18-64 years) with TRD ^a (N = 223)	Adults (aged 18-64 years) with recurring or single-episode (≥ 2 years), moderate to severe MDD and ESK response (N = 297) in <ul style="list-style-type: none"> • TRANSFORM-1 or • TRANSFORM-2
Study design	<ul style="list-style-type: none"> • Phase 3, double-blind, placebo-controlled study • Conducted at 39 sites in 5 countries 	<ul style="list-style-type: none"> • Phase 3, double-blind, placebo-controlled study • Conducted at 99 sites in 15 countries • Patients enrolled directly or transferred in • Direct-entry patients: 4-week SO <ul style="list-style-type: none"> › Treatment responders: 4-week, open-label IND (flexibly dosed ESK^b + a new OAD given daily) • Direct-entry patients with response in IND and transfer-entry patients: 12-week OPT • At end of OPT, patients with stable response and patients with stable remission separately randomized 1:1 to receive ESK + OAD or placebo + OAD during MNT

(Continued)

IMPORTANT SAFETY INFORMATION (CONTINUED) WARNINGS AND PRECAUTIONS (CONTINUED)

SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO® is available only through a restricted program called the SPRAVATO® REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

Important requirements of the SPRAVATO® REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO® is:
 - › Only dispensed and administered in healthcare settings.
 - › Patients treated in outpatient settings (e.g., medical offices and clinics) must be enrolled in the program.
 - › Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO®.
- Pharmacies must be certified in the REMS and must only dispense SPRAVATO® to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies, is available at www.SPRAVATOREMS.com or 1-855-382-6022.

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(TRANSFORM-1 [NCT02417064], TRANSFORM-2, TRANSFORM-3 [NCT02422186], SUSTAIN-1, SUSTAIN-2 [NCT02497287], TRD-3006 [NCT03434041]) (Figure 1).^{14,18,20-22}

Study Design

Patient status at the end of the parent study determines whether a patient enters into the 4-week induction phase (IND) or the long-term

optimization/maintenance phase (OP/M).¹⁴ During IND, patients self-administer esketamine as a flexible dose of 28 mg (only as a starting dose for patients ≥65 years), 56 mg, or 84 mg given twice weekly under supervision. During OP/M, which is of variable duration, patients receive flexible esketamine dosing.^{14,15} Eleven primary outcome measures include the number of participants experiencing TEAEs, changes in biomarkers (eg, systolic and diastolic blood pressure,

Table 1 (Continued). Pivotal Short- and Long-Term Studies of Esketamine Nasal Spray in Patients With TRD^{5-7,10,11,18}

Treatment	TRANSFORM-2		SUSTAIN-1			
	Flexibly dosed ESK ^b + OAD (n = 114)	Placebo + OAD (n = 109)	Stable remission at MNT day 1		Stable response at MNT day 1	
			Fixed dose ESK + OAD (n = 90)	Placebo + OAD (n = 86)	Fixed dose ESK + OAD (n = 62)	Placebo + OAD (n = 59)
Demographic & baseline clinical traits						
Age (years, mean [SD])	44.9 (12.6)	46.4 (11.1)	45.4 (12.1)	46.2 (11.2)	47.2 (11.0)	46.7 (9.8)
Age at MDD diagnosis (years, mean [SD])	32.1 (12.5)	35.3 (13.0)	32.5 (11.4)	33.4 (11.4)	36.2 (13.3)	34.0 (10.5)
Duration of current episode (weeks, mean [SD])	111.4 (124.3)	118.0 (187.4)	112.2 (171.3)	110.5 (147.4)	121.6 (193.9)	141.8 (254.4)
Female (n [%])	75 (65.8)	63 (57.8)	58 (64.4)	59 (68.6)	38 (61.3)	42 (71.2)
White (n [%])	106 (93.0)	102 (93.6)	80 (88.9)	76 (88.4)	57 (91.9)	55 (93.2)
Primary end points						
Δ MADRS score from baseline to end of week 4 (LS mean [SE]) ^c	-19.8 (1.3)	-15.8 (1.3)	-	-	-	-
Time to relapse in patients with stable remission in OPT (HR [95% CI]) ^d	-	-	0.49 (0.29-0.84; P = .003)	-	-	-

(Continued)

**IMPORTANT SAFETY INFORMATION (CONTINUED)
WARNINGS AND PRECAUTIONS (CONTINUED)**

Suicidal Thoughts and Behaviors in Adolescents and Young Adults: In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included adult and pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. SPRAVATO[®] is not approved in pediatric (<18 years of age) patients.

There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO[®] and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Please see additional Important Safety Information throughout and full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO[®].

Table 1 (Continued). Pivotal Short- and Long-Term Studies of Esketamine Nasal Spray in Patients With TRD^{5-7,10,11,18}

Treatment	TRANSFORM-2		SUSTAIN-1			
	Flexibly dosed ESK ^b + OAD (n = 114)	Placebo + OAD (n = 109)	Stable remission at MNT day 1		Stable response at MNT day 1	
			Fixed dose ESK + OAD (n = 90)	Placebo + OAD (n = 86)	Fixed dose ESK + OAD (n = 62)	Placebo + OAD (n = 59)
Key secondary end points						
Patients with clinical response to treatment [%] ^e	7.9	4.6	-	-	-	-
Δ SDS score day 1 to day 28 (difference of LS means [95% CI]) ^f	-4.0 [-6.3 to -1.6]	-	-	-	-	-
Δ PHQ-9 score day 1 to day 28 (difference of LS means [95% CI]) ^f	-2.4 [-4.2 to -0.7]	-	-	-	-	-
Time to relapse in patients with stable response (without remission) in OPT (HR [95% CI])	-	-	-	-	0.30 (0.16-0.55; P < .001)	-

ESK, esketamine nasal spray; IND, induction phase; LS mean, least squares mean; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MNT, maintenance phase; OAD, oral antidepressant; OPT, optimization phase; PHQ-9, 9-item Patient Health Questionnaire; SO, screening and observation phase; SDS, Sheehan Disability Scale; TRD, treatment-resistant depression.

^aHaving moderate to severe, nonpsychotic MDD and no response to ≥ 2 antidepressants in current depressive episode.¹⁰

^bGiven twice weekly at a dosage of 56 or 84 mg.¹⁰

^cMADRS scoring: 0-6, depressive symptoms absent; 7-17, mild depression; 18-34, moderate depression; 35-60, severe depression.

^dRelapse defined as 2 consecutive assessments yielding a MADRS score of ≥ 22 separated by a clinically relevant event indicative or suggestive of relapse.¹¹

^eResponse defined as a ≥ 50% reduction in MADRS score by day 2 of treatment that was sustained to day 28; one ≥ 25% reduction in MADRS score from day 1 permitted on day 8, 15, or 22.¹⁰

^fIn TRANSFORM-1, results for the first key secondary end point (percentage of patients with clinical response to treatment) were not significant. Consequently, the other 2 end points could not be formally evaluated. Numerical comparisons are given in this table.

IMPORTANT SAFETY INFORMATION (CONTINUED) WARNINGS AND PRECAUTIONS (CONTINUED)

Increase in Blood Pressure: SPRAVATO® causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours.

Approximately 8% to 19% of SPRAVATO®-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO® is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing SPRAVATO®, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO® outweigh its risk.

Assess BP prior to administration of SPRAVATO®. In patients whose BP is elevated prior to SPRAVATO® administration (as a general guide: >140/90 mmHg), a decision to delay SPRAVATO® therapy should take into account the balance of benefit and risk in individual patients.

Please see additional Important Safety Information throughout and full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

Table 2. Most Common AEs in Short-Term Studies of Esketamine Nasal Spray in Patients With TRD^{5-7,a}

Most common AEs ^b		
Adverse event	ESK + OAD (%) (n = 346)	Placebo + OAD (%) (n = 222)
Dissociation*	41	9
Dizziness*	29	8
Nausea	28	9
Sedation*	23	9
Vertigo*	23	3
Hypoesthesia*	18	2
Anxiety*	13	6
Lethargy*	11	5
Blood pressure increased*	10	3
Vomiting	9	2
Feeling drunk	5	0.5
Additional AEs ^c (ESK + OAD vs placebo + OAD)		
Headache* (20% vs 17%), dysgeusia* (19% vs 14%), insomnia (8% vs 7%), diarrhea (7% vs 6%), nasal discomfort* (7% vs 5%), throat irritation (7% vs 4%), dry mouth (5% vs 3%), hyperhidrosis (4% vs 2%), euphoric mood (4% vs 1%), dysarthria* (4% vs 0%), tremor (3% vs 1%), pollakiuria (3% vs 0.5%), feeling abnormal (3% vs 0%), tachycardia* (2% vs 0.5%).		

*The following terms were combined. **Dissociation includes:** delusional perception, depersonalization/derealization disorder, derealization, et al. **Dizziness includes:** dizziness, dizziness exertional, dizziness postural, procedural dizziness. **Sedation includes:** altered state of consciousness, hypersomnia, sedation, somnolence. **Vertigo includes:** vertigo, vertigo positional. **Hypoesthesia includes:** hypoesthesia, hypoesthesia oral, hypoesthesia teeth, pharyngeal hypoesthesia. **Anxiety includes:** agitation, anticipatory anxiety, anxiety, et al. **Lethargy includes:** fatigue, lethargy. **Blood pressure increased includes:** blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension. **Headache includes:** headache, sinus headache. **Dysgeusia includes:** dysgeusia, hypogeusia. **Nasal discomfort includes:** nasal crusting, nasal discomfort, nasal dryness, nasal pruritus. **Dysarthria includes:** dysarthria, slow speech, speech disorder. **Tachycardia includes:** extrasystoles, heart rate increased, tachycardia.

AE, adverse event; ESK, esketamine nasal spray; OAD, oral antidepressant; TRD, treatment-resistant depression.

^aPooled results from 5 phase 3 studies (including TRANSFORM-2 and SUSTAIN-1) and 1 phase 2 dose-ranging study.

^bAEs associated with ESK + OAD treatment with incidence ≥ 5% and at least twice that of placebo + OAD.

^cAEs associated with ESK + OAD treatment with incidence ≥ 2% and at a greater rate of placebo + OAD.

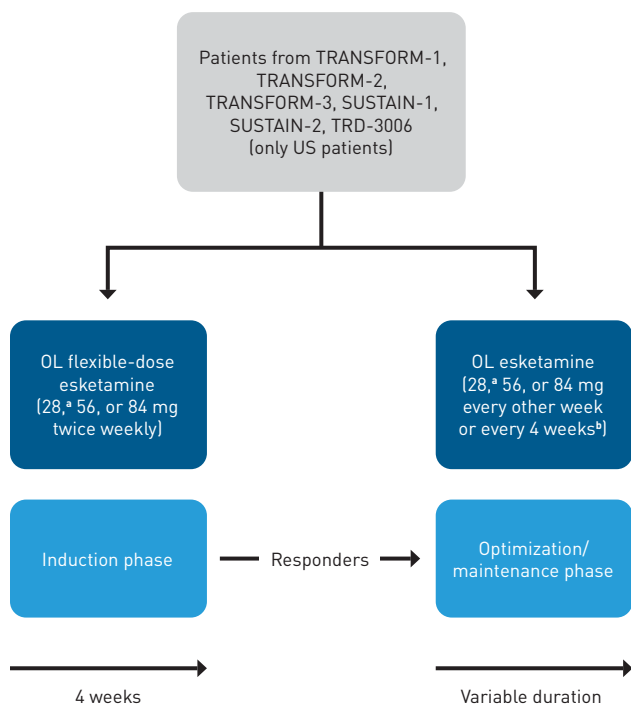
IMPORTANT SAFETY INFORMATION (CONTINUED) WARNINGS AND PRECAUTIONS (CONTINUED)

Increase in Blood Pressure (continued): BP should be monitored for at least 2 hours after SPRAVATO® administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness, or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO® with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) or monoamine oxidase inhibitors (MAOIs).

In patients with a history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Please see additional Important Safety Information throughout and full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

Figure 1. SUSTAIN-3 Study Design¹⁴

OL, open label.

^aThe 28-mg dose is only an option for patients aged ≥ 65 years.

^bBased on Clinical Global Impressions–Severity scale and tolerability.

Reproduced with permission from Zaki N, Nash AI, Chen N, et al. Long-term safety and sustenance of response with esketamine nasal spray in patients with treatment-resistant depression: SUSTAIN-3 interim results. Poster presented at: the Psych Congress 2021; October 29–November 1, 2021; San Antonio, TX.

baseline heart rate, and blood oxygen saturation), and changes in alertness, cognition, and suicidal ideation.¹⁵

Interim Subgroup Analyses

An interim subgroup analysis was conducted to evaluate the long-term efficacy of esketamine nasal spray plus OAD at up to 222 weeks (ie, 4 years, 14 weeks) in participants aged 18 to 64 years treated in accordance with US prescribing information.⁴ A second analysis evaluated the long-term safety of this combination in this subgroup.^{4,12}

In the interim efficacy analysis, changes in clinician-rated depressive symptoms were measured using the MADRS, changes in patient-rated depressive symptoms were measured with the PHQ-9, and changes in functional disability were measured using the SDS.^{4,23} Assessments of all 3 measures were performed at baseline. During IND, the MADRS was assessed weekly, the PHQ-9 results were reported every 2 weeks, and the SDS score was measured after 4 weeks. During OP/M, all 3 measures were assessed every 4 weeks.⁴ Changes in each of these outcome measures were summarized descriptively. At each end point, the percentage of patients who achieved response and remission were determined using MADRS (response, $\geq 50\%$ improvement from baseline; remission, score ≤ 12) and PHQ-9 (response, $\geq 50\%$ improvement from baseline; remission, score < 5).⁴

In the interim safety analysis, TEAEs, serious AEs, clinical laboratory test results, and cognitive test results (from the Hopkins Verbal Learning Test–Revised and the CogState Computerized Test Battery) were assessed on dosing days over IND and OP/M and then summarized.¹²

Interim Results: Long-Term Efficacy and Safety of Esketamine

In the SUSTAIN-3 subgroup analysis population (N = 1006), 43.3% of patients entered at IND; the remainder (56.7%) entered at OP/M.⁴ Patients' mean (SD) age was 47.3 (10.7) years, and approximately two-thirds (66.5%) were women. Most patients were White (85.9%),

IMPORTANT SAFETY INFORMATION (CONTINUED) WARNINGS AND PRECAUTIONS (CONTINUED)

Cognitive Impairment

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 the 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 repeated ketamine misuse or abuse. No adverse effects of SPRAVATO[®] nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO[®] have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery: 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. Patients will need to arrange transportation home following treatment with SPRAVATO[®].

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and most identified as not Hispanic or Latino (79.4%). Mean (SD) age at MDD diagnosis was 32.8 (11.9) years, and mean (SD) duration of the current MDD episode was about 3 (4.5) years.⁴

Over the combined course of IND and OP/M, most patients (68.9%) were treated with esketamine for at least 30 months; mean exposure to esketamine during this period was approximately 2.4 (1.1) years.⁴

Efficacy

At IND baseline, the mean (SD) MADRS and PHQ-9 scores were consistent with moderately severe disease (MADRS, 29.1 [8.0]; PHQ-9, 15.4 [5.6]) (Figure 2).^{4,24} From baseline to the end of IND (last observation carried forward [LOCF]), both disease severity scores fell; mean (SD) changes in MADRS and PHQ-9 scores were -12.8 (9.7) and -5.9 (5.8), respectively.⁴ This reduction was largely sustained throughout OP/M (LOCF); from OP/M baseline to last assessment, mean (SD) changes in disease severity scores were relatively small (MADRS, 1.1 [10.2]; PHQ-9: 0.8 [6.1]) (Figure 2).⁴ At the end of IND, 50.3% (n/N, 218/433) of patients achieved response and 36.5% (158/433) achieved remission according to MADRS scores; according to PHQ-9 scores, 38.4% (165/430) achieved response and 20.4% (88/432) achieved remission. During the last assessment in OP/M, 46.0% (446/970) and 31.5% (306/970) of patients achieved remission as assessed by MADRS scores and PHQ-9 scores, respectively.⁴

During IND (LOCF), the mean change (SD) in SDS total score from baseline through end point was -6.4 (7.2). This reduction was generally maintained through OP/M (LOCF); from OP/M baseline to the last assessment, mean (SD) changes in SDS total score were relatively small (-0.1 [8.3]).⁴

Safety

Throughout IND and OP/M, 93.5% of patients experienced at least 1 TEAE. Most (96.7%) TEAEs emerged and resolved on the day of dosing; the majority were of mild or moderate severity.¹²

Headache was the most common TEAE and occurred in 33.9% of patients. Dizziness (in 32.0% of patients), nausea (32.0%), dissociation (25.6%), somnolence (23.4%), nasopharyngitis (22.3%), and dysgeusia (20.9%) were also common.¹²

During IND and OP/M, 0.7% (n/N, 3/436) and 14.3% (139/971) of patients experienced at least 1 serious AE, respectively. AEs caused treatment withdrawal in 1.1% (5/436) and 5.1% (50/971) of patients during IND and OP/M, respectively.¹²

Throughout IND and OP/M, 6.0% (n = 60) of patients experienced at least 1 TEAE related to suicidality. These TEAEs included suicidal ideation (n = 44), suicidal depression (n = 1), suicidal behavior (n = 3), attempted suicide (n = 11), and completed suicide (n = 1). Investigators considered neither the completed suicide nor the 2 other deaths that occurred during these phases (from COVID-19 and multiple injuries, respectively) related to esketamine.¹²

Study limitations

Study authors acknowledged several limitations, including the lack of a control group in the SUSTAIN-3 trial, which is open label. Moreover, the findings of this interim analysis may have limited generalizability; patients with significant psychiatric or medical comorbidities or substance dependence were excluded, sample sizes decreased over time, and patient choice to continue (or not to continue) from the parent study may have introduced bias.^{4,12}

CONCLUSIONS

In this interim subgroup analysis, open-label treatment with esketamine nasal spray plus an OAD in patients with TRD aged 18 to 64 years was associated with safety and efficacy results consistent with those seen in the short-term TRD trials.⁴ The safety and tolerability profile of this combination during this period was consistent with the profile

IMPORTANT SAFETY INFORMATION (CONTINUED) WARNINGS AND PRECAUTIONS (CONTINUED)

Ulcerative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO[®] nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO[®]-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO[®] and refer to an appropriate healthcare provider as clinically warranted.

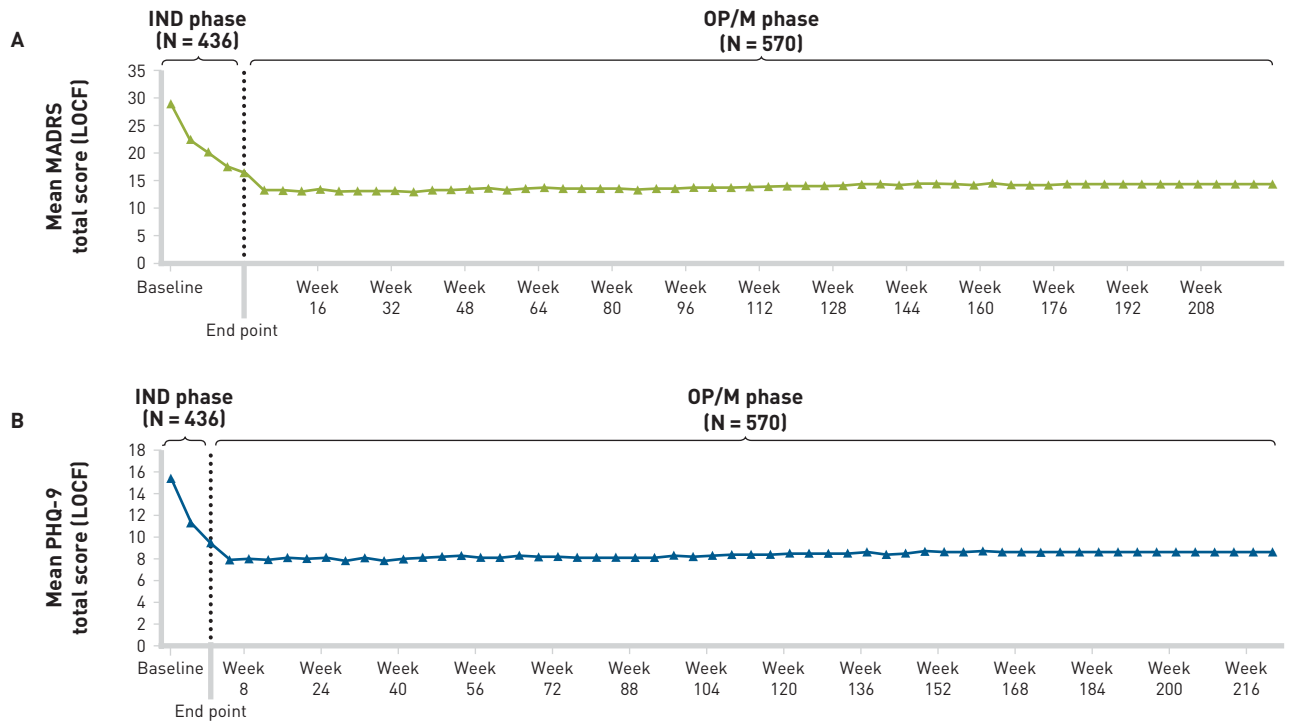
PREGNANCY, EMBRYO-FETAL TOXICITY, AND LACTATION

SPRAVATO[®] is not recommended during pregnancy. SPRAVATO[®] may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO[®] *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention.

There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO[®], treatment with SPRAVATO[®] should be discontinued and the patient should be counseled about the potential risk to the fetus.

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Figure 2. (A) Mean MADRS and (B) PHQ-9 Total Scores (LOCF) During the Induction and Optimization/Maintenance Phases of the SUSTAIN-3 Study^{4,24,a,b}



IND induction; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M optimization/maintenance; PHQ-9, 9-item Patient Health Questionnaire.

^aMADRS scoring: 0-6, depressive symptoms absent; 9-17, mild depression; 18-34, moderate depression; 35-60, severe depression.^{4,24}

^bN-size: ≥ 1 year (n = 817), ≥ 2 years (n = 738), ≥ 3 years (n = 481), and ≥ 4 years (n = 6) of SPRAVATO[®] exposure. Because SUSTAIN-3 is an ongoing study, proportions of patients with ≥ 3 years and ≥ 4 years of exposure are expected to increase with time and do not currently reflect discontinuations related to SPRAVATO tolerability.⁴

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**IMPORTANT SAFETY INFORMATION (CONTINUED)
PREGNANCY, EMBRYO-FETAL TOXICITY, AND LACTATION (CONTINUED)**

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO[®], during pregnancy.

Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.

SPRAVATO[®] is present in human milk. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO[®].

SELECT USE IN SPECIFIC POPULATIONS

Geriatric Use: No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age. At the end of a 4-week, randomized, double-blind study, there was no statistically significant difference between groups on the primary efficacy endpoint.

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established by shorter-term studies.⁵⁻¹² Most TEAEs were of mild or moderate severity and were resolved within a day after dosing.¹² These findings provide additional data to help inform treatment decisions surrounding TRD, a medical condition associated with high levels of clinical, economic, and humanistic burden.^{1,2}

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IMPORTANT SAFETY INFORMATION (CONTINUED) SELECT USE IN SPECIFIC POPULATIONS (CONTINUED)

Hepatic Impairment: SPRAVATO®-treated patients with moderate hepatic impairment 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.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence $\geq 5\%$ and at least twice that of placebo nasal spray plus oral antidepressant) were:

TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

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