Weight and Metabolic Changes in Patients Treated With Esketamine Nasal Spray Versus Quetiapine Extended Release: A Post Hoc Subgroup Analysis of the ESCAPE-TRD Study

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Introduction

- Esketamine nasal spray (ESK) is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist approved in the US, in conjunction with an oral antidepressant (OAD), for the treatment of treatment-resistant depression (TRD) in adults and for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior[1]
- In ESCAPE-TRD (NCT04338321), a randomized, open-label, rater-blinded phase 3b trial investigating ESK versus quetiapine extended release (QXR) both in conjunction with an OAD in patients with TRD, patients treated with ESK had higher remission and response rates over 32 weeks of treatment compared with QXR[2]
- Weight gain and metabolic changes are common side effects of OADs and atypical antipsychotics, including QXR[3-5]
- In this subgroup analysis, patients from ESCAPE-TRD whose treatment was consistent with US prescribing information were selected, thereby delivering a study of greater value to healthcare providers, patients, and decision-makers in the US and providing guidance to ensure the safe, effective, and appropriate administration of ESK

Objective

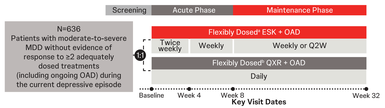
- To describe weight and metabolic changes associated with ESK versus QXR in patients with TRD from ESCAPE-TRD, and their impact on study outcomes

Methods

Study design and participants

- Patients included in this ESCAPE-TRD subgroup analysis were 18-64 years old and received at least 1 dose of the study intervention, flexibly dosed ESK (56 or 84 mg) or QXR, dosed according to US prescribing information, and in combination with an ongoing OAD (**Figure 1**)
- The treatment period consisted of an 8-week acute phase followed by a 24-week maintenance phase (**Figure 1**)

FIGURE 1. ESCAPE-TRD study design



ESK, esketamine nasal spray; MDD, major depressive disorder; OAD, oral antidepressant; Q2W, every other week, QXR, quetiapine extended release.
[a]ESK was dosed twice weekly (56 mg on day 1, increased to 56/84 mg from day 4) from weeks 1 to 4, weekly (56/84 mg) from weeks 5 to 8, and weekly or Q2W (56/84 mg) from weeks 9 to 32, all in addition to an ongoing OAD that elicited non-response at baseline.
[b]QXR was dosed daily, starting at 50 mg and titrated up to ≥150 mg by the end of week 2, and was then flexibly dosed (150-300 mg/day) from weeks 3 to 32, all in addition to an ongoing OAD that elicited non-response at baseline.

Data analyses

- Baseline differences between treatment groups were assessed using *t* tests for continuous variables and chi-square tests for categorical variables
- Patients were assessed by treatment arm and by body mass index (BMI) category (underweight, BMI <18.5; normal, BMI 18.5-24; overweight, BMI 25-29; obese, BMI 30-35; morbidly obese, BMI >35) at different time points of treatment (weeks 8 and 32). End point data include the last assessment of the study for patients who received at least 1 dose of study intervention
- Within-group mean changes in weight and BMI were analyzed using paired *t* tests, while between-group comparisons were conducted using analysis of covariance (ANCOVA) models, incorporating fixed effects for treatment group, age, total number of prior treatment failures, and the corresponding baseline value as a covariate
- Weight-related adverse events were considered treatment-emergent if they occurred between the first dose and 14 days after the last dose of study medication. The proportion of patients experiencing weight-related treatment-emergent adverse events (TEAEs) was reported
- Clinically significant weight gain was defined as an increase of ≥7% in body weight. The proportion of patients experiencing clinically significant weight gain between treatment groups was compared using the Cochran-Mantel-Haenszel test, controlling for randomization factors of age and total number of treatment failures
- Shifts in the proportion of patients across BMI categories from baseline to the study end point were reported
- Mean changes from baseline in clinical laboratory values, as well as changes in Montgomery-Åsberg Depression Rating Scale (MADRS) total score by BMI level, were assessed using paired *t* tests within treatment groups and ANCOVA models for between-group comparisons

Results

Patient baseline characteristics

- This analysis included a total of 630 patients (ESK, n = 314; QXR, n = 316) (**Table 1**)
- Baseline characteristics were comparable between study arms, including demographics and psychiatric history (**Table 1**)
- Baseline mean weight and BMI were significantly higher at baseline in the QXR arm compared with the ESK arm ($P < 0.05$) (**Table 1**)

TABLE 1. Baseline demographic and clinical characteristics[a]

	ESK + OAD n = 314	QXR + OAD n = 316
Baseline demographics		
Mean age (SD), years	42.8 (12.6)	44.5 (12.5)
Female, n (%)	211 (67.2)	205 (64.9)
Race, n (%)	n = 142	n = 159
Asian	8 (5.6)	10 (6.3)
Black or African American	4 (2.8)	6 (3.8)
White	130 (91.6)	143 (89.9)
Ethnicity, n (%)	n = 140	n = 160
Hispanic/Latino	27 (19.3)	34 (21.3)
Not Hispanic/Latino	113 (80.7)	126 (78.8)
Baseline weight		
Mean weight (SD), kg*	76.4 (16.4)	79.4 (16.8)
Baseline BMI[b]		
Mean BMI (SD)*	26.5 (4.9)	27.5 (5.1)
BMI category, n (%)		
Underweight (BMI <18.5)	6 (2.3)	5 (1.9)
Normal (BMI 18.5 to <25)	105 (40.2)	84 (31.6)
Overweight (BMI 25 to <30)	89 (34.1)	89 (33.5)
Obese (BMI 30 to 35)	40 (15.3)	71 (26.7)
Morbidly obese (BMI >35)	21 (8.1)	17 (6.4)
Psychiatric history		
Mean age when diagnosed with MDD (SD), years	33.0 (11.6)	34.5 (11.7)
Mean duration of current episode (SD), weeks	67.9 (85.4)	63.1 (62.7)
Mean baseline MADRS total score (SD)	31.6 (6.0)	31.1 (5.9)
Mean baseline PHQ-9 total score (SD)	17.9 (4.3)	17.4 (4.5)
Mean baseline CGI-S score (SD)	4.9 (0.6)	4.9 (0.7)

BMI, body mass index; CGI-S, Clinical Global Impression-Severity scale; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; PHQ-9, 9-Item Patient Health Questionnaire; QXR, quetiapine extended release.
[a]Height data were not available for all patients, and therefore patient numbers are smaller for BMI compared with weight assessments (ESK, n=281; QXR, n=266).
*$P < 0.05$.

Weight-related TEAEs

- More QXR-treated patients reported TEAEs related to increased weight compared with ESK-treated patients (12.3% vs 2.9%, respectively) (**Table 2**)
- Furthermore, TEAEs related to increased weight led to treatment discontinuation in 1.6% (n = 5) of QXR-treated patients, with no patients in the ESK group discontinuing the study due to a weight-related TEAE (**Table 2**)

TABLE 2. Summary of weight-related TEAEs

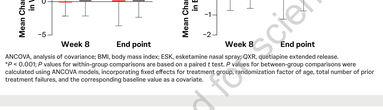
	ESK + OAD n = 314	QXR + OAD n = 316
Total TEAEs, n (%)	289 (92.0)	248 (78.5)
Weight-related TEAEs by MedDRA preferred term		
Weight increased, n (%)	9 (2.9)	39 (12.3)
Weight decreased, n (%)	7 (2.2)	0 (0.0)
Total TEAEs leading to study drug withdrawal, n (%)	14 (4.5)	32 (10.1)
Weight-related TEAE leading to discontinuation		
Weight increased, n (%)	0 (0.0)	5 (1.6)

ESK, esketamine nasal spray, MedDRA, Medical Dictionary for Regulatory Activities; OAD, oral antidepressant; QXR, quetiapine extended release; TEAE, treatment-emergent adverse event.
TEAEs occurred between the first dose and up to 14 days after the last dose of study medication.

Changes in weight and BMI

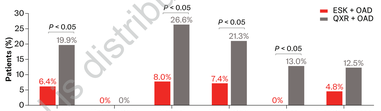
- Patients treated with QXR exhibited significant mean increases in both weight and BMI at week 8 and at study end point compared to baseline ($P < 0.001$), while those treated with ESK did not show significant mean changes (**Figure 2**)
- The difference in mean weight change and BMI between QXR- and ESK- treated patients were also statistically significant at week 8 and at study end point ($P < 0.001$) (**Figure 2**)
- At study end point, more QXR-treated patients had clinically significant weight gain (≥7% increase) compared with ESK-treated patients overall and by BMI category (**Figure 3**)
- Similarly, more QXR-treated patients shifted to a higher BMI category during their treatment compared with ESK-treated patients, for all BMI categories (**Table 3**)

FIGURE 2. Mean (SD) change from baseline in patient (A) weight and (B) BMI at week 8 and study end point



ANCOVA, analysis of covariance; BMI, body mass index; ESK, esketamine nasal spray; QXR, quetiapine extended release.
*$P < 0.001$. P values for within-group comparisons are based on a paired t test. P values for between-group comparisons were calculated using ANCOVA models, incorporating fixed effects for treatment group, randomization factor of age, total number of prior treatment failures, and the corresponding baseline value as a covariate.

FIGURE 3. Proportion of patients with clinically significant weight gain (≥7%) at study end point by BMI category



BMI, body mass index; ESK, esketamine nasal spray; QXR, quetiapine extended release.
P values are based on a Cochran-Mantel-Haenszel test controlling for randomization factors of age and total number of treatment failures.

TABLE 3. Shift in proportion of patients in each BMI category from baseline to study end point

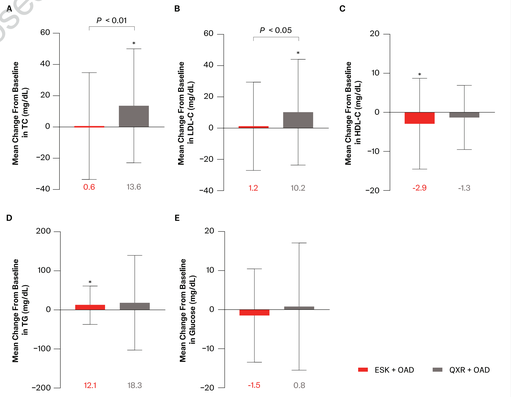
	ESK + OAD, %					QXR + OAD, %					
	BMI category at baseline					BMI category at baseline					
BMI category at endpoint	Underweight (n = 5)	Normal (n = 100)	Overweight (n = 81)	Obese (n = 38)	Morbidly Obese (n = 21)	Underweight (n = 4)	Normal (n = 79)	Overweight (n = 80)	Obese (n = 69)	Morbidly Obese (n = 16)	
Underweight	80.0	1.0	0.0	0.0	0.0	75.0	0.0	0.0	0.0	0.0	BMI decreased
Normal	20.0	87.0	18.5	0.0	0.0	25.0	75.9	0.0	0.0	0.0	
Overweight	0.0	12.0	77.7	13.1	0.0	0.0	22.7	77.5	13.0	0.0	
Obese	0.0	0.0	3.7	78.9	14.2	0.0	1.2	22.5	73.9	12.5	
Morbidly Obese	0.0	0.0	0.0	7.8	85.7	0.0	0.0	0.0	13.0	87.5	BMI increased

BMI, body mass index; ESK, esketamine nasal spray; OAD, oral antidepressant; QXR, quetiapine extended release.

Metabolic changes

- Clinical laboratory values were assessed for ESK- and QXR-treated patients at week 32, including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and glucose (**Figure 4**)
- Both total cholesterol and low-density lipoprotein cholesterol were significantly increased from baseline at week 32 in QXR-treated patients ($P \leq 0.05$) and significantly increased compared to ESK-treated patients ($P \leq 0.05$) (**Figure 4**)

FIGURE 4. Mean (SD) change from baseline in clinical laboratory values at week 32 of treatment

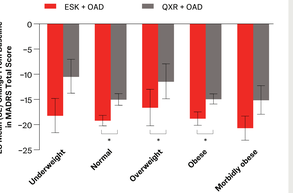


ANCOVA, analysis of covariance; ESK, esketamine nasal spray; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OAD, oral antidepressant; QXR, quetiapine extended release; TC, total cholesterol; TG, triglycerides.
*$P \leq 0.05$; P values for within-group comparisons are based on a paired t test. P values for between-group comparisons were calculated using an ANCOVA model with fixed effects for treatment group, randomization factors of age and total number of treatment failures, and baseline value as a covariate.

Efficacy by BMI category

- ESK-treated patients demonstrated greater improvement in MADRS total scores compared to QXR-treated patients at study end point in all BMI categories (**Figure 5**)

FIGURE 5. LS mean (SE) change from baseline in MADRS total score by BMI category at study end point



ESK + OAD, n	5	103	86	40	21
QXR + OAD, n	5	82	88	71	16

ANCOVA, analysis of covariance; BMI, body mass index; ESK, esketamine nasal spray; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; OAD, oral antidepressant; QXR, quetiapine extended release; SE, standard error.
*$P \leq 0.05$; Least squares means and P values for between-group comparisons are from an ANCOVA model with fixed effects for treatment group, randomization factors of age and total number of treatment failures, and baseline BMI score and baseline score as covariates.

Key Takeaway

Treatment with ESK is associated with fewer weight-related TEAEs, less weight gain, fewer metabolic changes, and fewer weight-related treatment discontinuations compared with QXR

Limitations

- The small sample size in the underweight and morbidly obese (BMI >35) categories may limit the generalizability of results for these patient populations
- Differences in routes of administration, treatment adherence, and frequency and duration of study visits between treatment arms could potentially introduce bias into the results

Conclusions

- Fewer patients treated with ESK experienced weight-related TEAEs and weight-related TEAEs that led to treatment discontinuation compared with QXR-treated patients
- Patients treated with QXR had significant increases in weight and BMI, and a higher proportion of patients experienced clinically significant weight gain (≥7% increase) compared with ESK-treated patients
- QXR-treated patients experienced a significant increase in mean total and low-density lipoprotein cholesterol compared with ESK-treated patients
- ESK-treated patients had greater improvement in MADRS total scores compared with QXR-treated patients, regardless of BMI category

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References
1. SPRAVATO® (esketamine) nasal spray, CIII. Package insert. Janssen Pharmaceuticals, Inc.; 2023. Accessed September 18, 2024. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf **2.** Reif A et al. *N Engl J Med*. 2023;389(14):1298-1309. **3.** Bak M et al. *PLoS One*. 2014;9(4):e94112. **4.** Carr CN et al. *Ment Health Clin*. 2016;6(6):308-313. **5.** Sepúlveda-Lizcano L et al. *Eur J Investig Health Psychol Educ*. 2023;13(8):1505-1520.

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