Long-Term Safety and Efficacy of Esketamine Nasal Spray in Adults With Treatment-Resistant Depression: A Post Hoc Analysis of ESCAPE-LTE

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Introduction

- ESCAPE-TRD (NCT04338321) was a 32-week, randomized, phase 3b trial comparing the safety and efficacy of flexibly dosed esketamine nasal spray (ESK) vs quetiapine extended-release, both given in conjunction with a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI), in adults with treatment-resistant depression (TRD)[1]
- Primary and secondary analyses of the ESCAPE-TRD study demonstrated superiority of ESK over quetiapine extended-release[1-3]
- ESCAPE-LTE (NCT04829318) was a long-term, open-label extension, phase 4 study for patients who were continuing ESK treatment in combination with an SSRI/SNRI following ESCAPE-TRD[4]
- In this post hoc analysis, we evaluate the long-term safety and efficacy of ESK among patients in ESCAPE-LTE who were 18-64 years old and received ESK dosed according to US prescribing information (i.e., flexibly dosed ESK 56 mg or 84 mg)[5]

Methods

Study design

- ESCAPE-LTE was a single-arm, 2-year (104-week), open-label extension to patients in 14 countries who had participated in ESCAPE-TRD
- Patients who completed maintenance ESK treatment in combination with an SSRI/SNRI to week 32 in ESCAPE-TRD were eligible to continue ESK treatment in ESCAPE-LTE (**Figure 1**). ESK dose and frequency could be adjusted within label recommendations based on the investigator's clinical judgement

End Points

- Safety end points included assessment of treatment-emergent adverse events (TEAEs)
- Efficacy end points included
  - Mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to week 136
  - Percentage of patients with evidence of response or remission based on MADRS total score at baseline and at week 136
  - Percentage of patients who were relapse free at week 136 among patients who were in remission at week 8

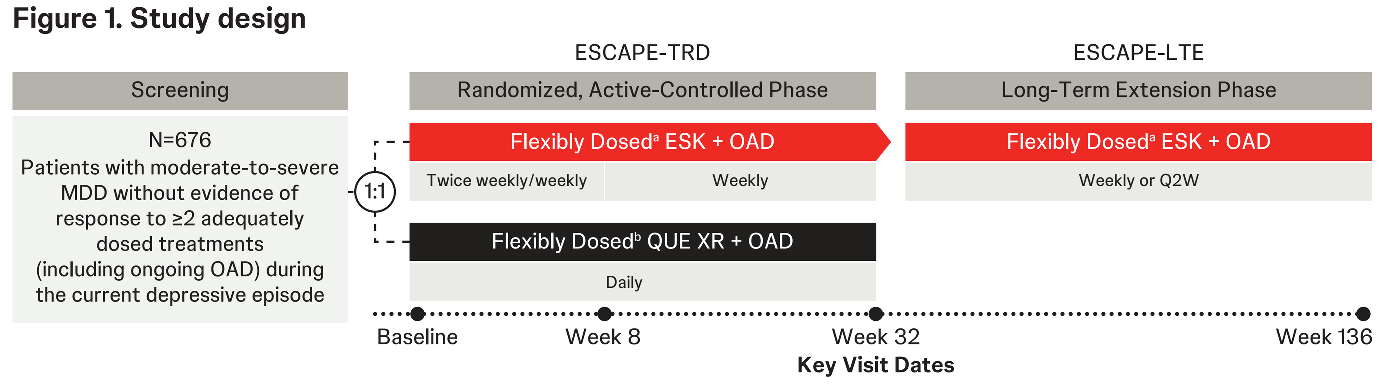
Assessments

- Response was defined as ≥50% improvement from baseline in MADRS total score
- Remission was defined as MADRS total score ≤12 or MADRS total score ≤10 (protocol-defined remission)
- Relapse was defined as MADRS total score ≥22 at 2 consecutive assessments within 5 to 31 days of each other; hospitalization for worsening depression, suicide prevention, or suicide attempt; or any other event assessed as indicative of relapse

Analyses

- Patients included in this analysis were aged 18-64 years and received flexibly dosed ESK (56 or 84 mg) in combination with an SSRI/SNRI, consistent with US prescribing information[5]
- Analyses were conducted using the safety/efficacy analysis set, which comprised all patients who received at least 1 dose of study treatment during ESCAPE-LTE
- Statistics are summarized descriptively

Figure 1. Study design



ESK, esketamine nasal spray; MDD, major depressive disorder; OAD, oral antidepressant; Q2W, every other week; QUE XR, quetiapine extended-release.
[a]ESK was dosed twice weekly during weeks 1-4, weekly during weeks 5-8, and weekly or Q2W during weeks 9-32, all in addition to ongoing treatment with an OAD. In the long-term extension phase, ESK was dosed weekly or Q2W; investigators could change the dose and frequency within label recommendations based on clinical judgement.
[b]QUE XR was dosed once daily, titrating up to ≥150 mg/day by the end of week 2, then flexibly dosed at 150 to 300 mg/day to week 32, all in addition to ongoing treatment with an OAD.

Results

Baseline demographics and disease characteristics

- Among 316 patients randomly assigned to receive ESK in ESCAPE-TRD, 175 patients went on to receive ESK in ESCAPE-LTE and were dosed according to US prescribing information
- Baseline demographic and disease characteristics are shown in **Table 1**

Table 1: Baseline characteristics

	ESCAPE-LTE n = 175
Mean age (SD), years	43.5 (12.2)
Female, n (%)	121 (69.1)
Number of prior antidepressant trials, n (%)	
2	118 (67.4)
≥3	57 (32.6)
Mean age at MDD diagnosis (SD), years	34.2 (11.2)
Mean baseline MADRS total score (SD)	31.6 (5.6)
Mean duration of current episode (SD), weeks	52.4 (52.1)

MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder.

Safety

- A total of 155 patients (88.6%) experienced TEAEs during ESCAPE-LTE and 161 patients (92.0%) experienced TEAEs during ESCAPE-TRD (**Table 2**)
- TEAEs considered possibly related to study treatment occurred in 123 (70.3%) and 151 (86.3%) patients in ESCAPE-LTE and ESCAPE-TRD, respectively
- The percentage of patients who experienced serious TEAEs or TEAEs that led to study drug withdrawal or dose interruptions or modifications were low (**Table 2**). One patient experienced a TEAE that resulted in death because of multiple injuries that were unrelated to the study treatment
- The most common TEAEs during ESCAPE-LTE and ESCAPE-TRD were dizziness, headache, and nausea. Most TEAEs that occurred on dosing days were resolved on the same day

Change in MADRS total score

- Mean (SD) MADRS total score decreased from 31.6 (5.6) at baseline to 9.3 (6.2) at week 32, consistent with a previous analysis of the total study population in ESCAPE-TRD[1] (**Figure 2**)
- Improvements in MADRS total score continued during ESCAPE-LTE through week 136, with a mean (SD) MADRS total score of 6.9 (5.3), representing a mean (SD) change from baseline total score of −25.3 (6.8). These results were consistent with a previous analysis of the total study population in ESCAPE-LTE[4] (**Figure 2**)

Response and remission

- At week 32 (n = 174), 87.9% of patients had evidence of response and 77.0% had evidence of remission (defined as MADRS total score ≤12). Over the course of ESCAPE-LTE, response and remission rates increased, with 95.0% of patients having evidence of response and 86.8% of patients having evidence of remission by week 136 (n = 121) (**Figure 3**)

Table 2: Safety summary

Patients experiencing TEAEs, n (% [95% CI])	ESCAPE-TRD n = 175	ESCAPE-LTE n = 175
All TEAEs	161 (92.0 [86.9, 95.6])	155 (88.6 [82.9, 92.9])
TEAEs possibly related to study drug	151 (86.3 [80.3, 91.0])	123 (70.3 [62.9, 77.0])
TEAEs leading to death	0	1 (0.6 [0.0, 3.1])[a]
≥1 serious TEAE	4 (2.3 [0.6, 5.8])	11 (6.3 [3.2, 11.0])
TEAE leading to study drug withdrawal	0	6 (3.4 [1.3, 7.3])
TEAE leading to dose interruption or modifications	19 (10.9 [6.7, 16.4])	22 (12.6 [8.1, 18.4])
Most frequent (>20%) TEAEs, n (%)		
Headache	59 (33.7)	81 (46.3)
Dizziness	73 (41.7)	49 (28.0)
Nausea	59 (33.7)	36 (20.6)
Nasopharyngitis	10 (5.7)	35 (20.0)
Vertigo	43 (24.6)	30 (17.1)
Dissociation	40 (22.9)	19 (10.9)

TEAEs, treatment-emergent adverse events.
[a]One patient experienced a TEAE leading to death because of multiple injuries that were unrelated to the study treatment.

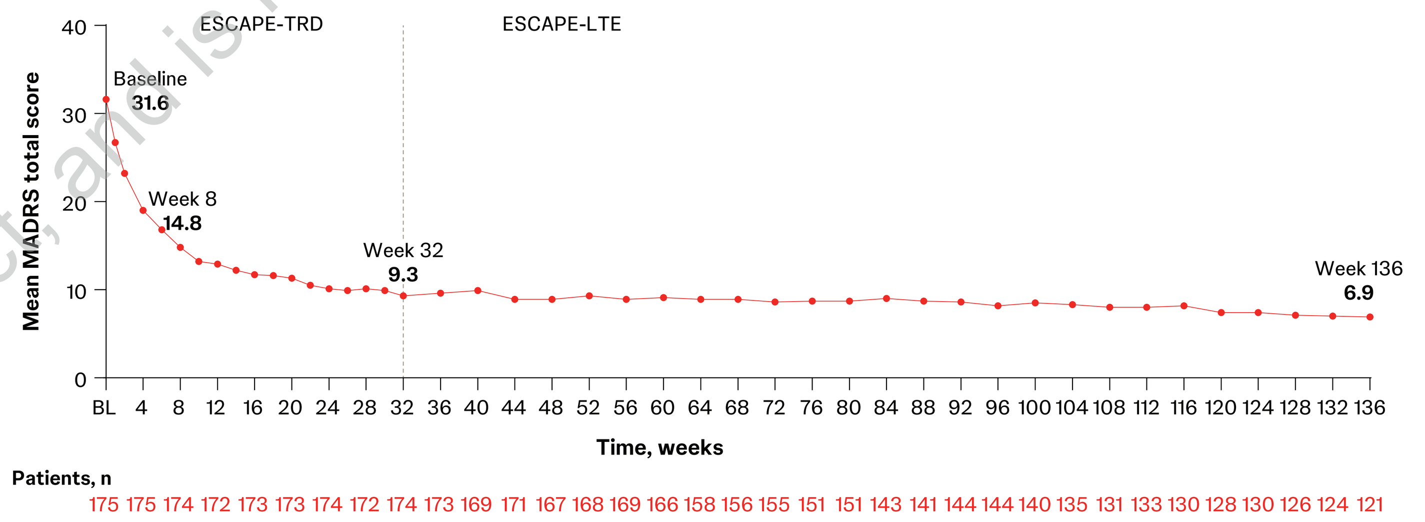
Relapse

- Of the 50 patients who had evidence of protocol-defined remission (MADRS total score ≤10) at week 8 of ESCAPE-TRD, 44 (88.0%) did not have evidence of relapse from the point of remission through the end of the ESCAPE-LTE study, at week 136. These results were consistent with a previous analysis of ESCAPE-TRD, in which 80.2% of patients who achieved protocol-defined remission at week 8 were relapse free to the end of the study at week 32[1]
- A total of 22 patients who were not in protocol-defined remission during ESCAPE-TRD attained protocol-defined remission in ESCAPE-LTE; of these, 19 (86.4%) did not have evidence of relapse

Limitations

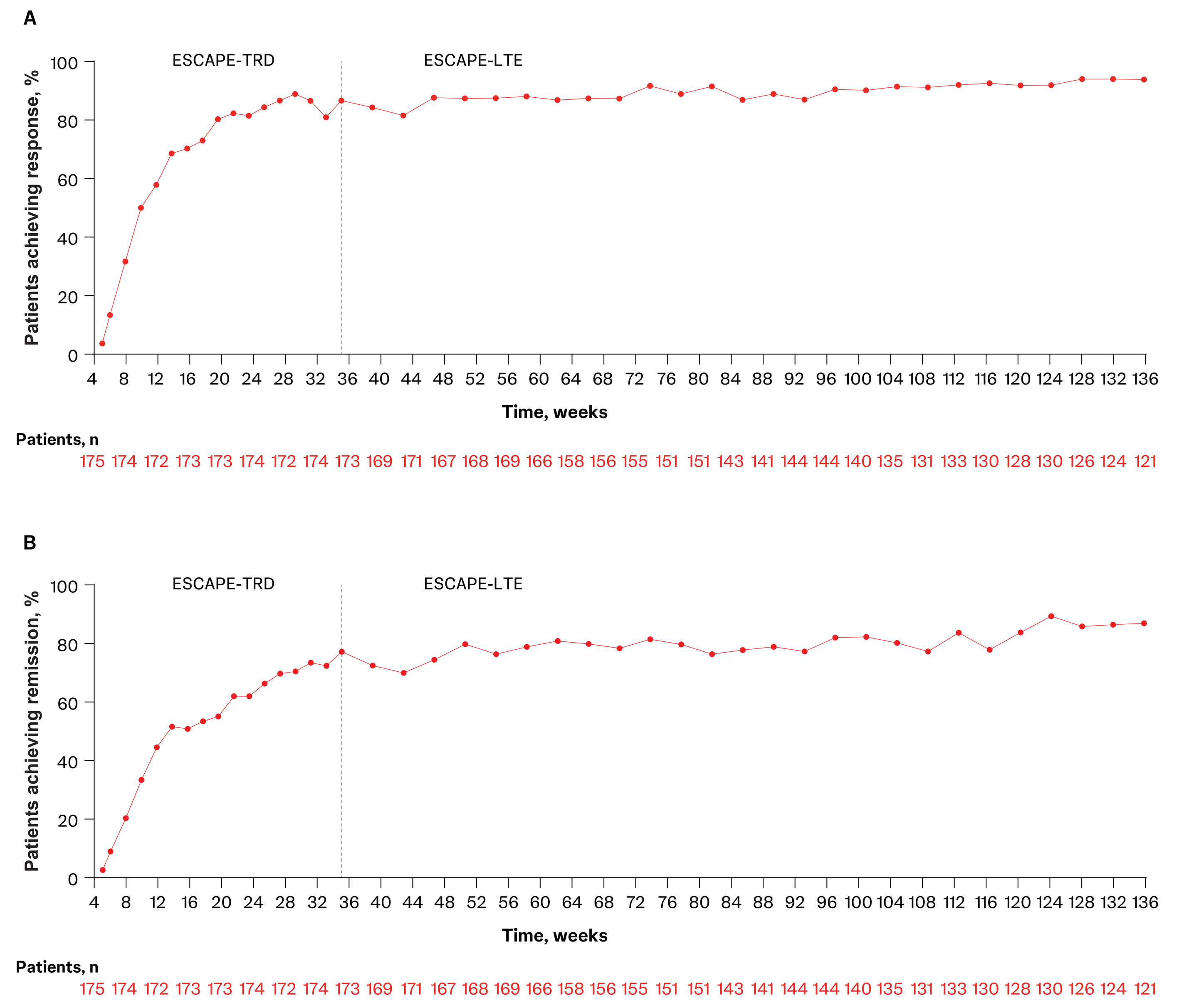
- This analysis included an enriched population of patients who completed ESCAPE-TRD and continued to benefit from ESK treatment
- Only patients from countries where ESK was not accessible or reimbursable were able to enter ESCAPE-LTE
- ESCAPE-LTE was an open-label extension study with no comparator

Figure 2: Change in MADRS total score over 136 weeks in ESCAPE-TRD and ESCAPE-LTE



BL, baseline; MADRS, Montgomery-Åsberg Depression Rating Scale.

Figure 3: Percentage of patients achieving response (A) and remission (B) over 136 weeks in ESCAPE-TRD and ESCAPE-LTE



MADRS, Montgomery-Åsberg Depression Rating Scale.
Response was defined as ≥50% improvement from baseline in MADRS total score; remission was defined as MADRS total score ≤12.

Key Takeaways

These data demonstrate the long-term safety and efficacy of ESK in patients with TRD who were administered ESK according to US prescribing information for up to 136 weeks

Substantial and sustained improvements in MADRS total scores, response rates, and remission rates, combined with low relapse rates, demonstrate the efficacy of ESK in reducing depressive symptoms for patients with TRD

Conclusions

Safety results were consistent with the established safety and tolerability profile of esketamine nasal spray, with no new safety signals identified

Treatment with esketamine nasal spray in combination with an oral antidepressant was associated with long-term improvements in depressive symptoms, as measured by MADRS total score, up to 136 weeks

Acknowledgements
The authors thank Lynn Brown, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Johnson & Johnson.

Disclosures
MH, OL, LL, IT, IVU, and YG are employees of Johnson & Johnson, and may hold stock in Johnson & Johnson.

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This study was funded by Johnson & Johnson.

Presented at Neuroscience Education Institute (NEI) Fall Congress; November 6-9, 2025; Colorado Springs, Colorado, USA

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