# Top-line Results from ESCAPE-LTE: An Open-Label Extension Study to Assess Long-term Safety of Esketamine Nasal Spray in Treatment Resistant Depression

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# Key Takeaways

- These data provide evidence to support **esketamine NS safety and efficacy in the long-term** treatment of patients with TRD.
- The **low relapse rate of 6.9%** and substantial and sustained **reductions in mean MADRS scores** over time **demonstrate efficacy of esketamine NS in reducing symptoms** for patients with TRD, which may allow patients to achieve a better quality of life in the long term.
- **Efficacy outcomes were maintained for most patients over 136 weeks** in ESCAPE-TRD and ESCAPE-LTE with **low relapse rates over the long term** and continuous improvements in mean MADRS score observed over time.
- **No new safety signals** in the long term.

# Background

- ESCAPE-TRD (NCT04338321) was a **32-week, randomised, phase IIIb trial** comparing the efficacy and safety of esketamine nasal spray (NS) versus quetiapine extended release (XR), when both were flexibly dosed alongside an ongoing selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI), **in patients with treatment resistant depression** (TRD).[1]
  - The study demonstrated that **esketamine NS significantly increased the probability of achieving remission at Week 8, and of being relapse-free through Week 32** after remission at Week 8, versus quetiapine XR.[1]
- ESCAPE-LTE was a **phase IV, long-term, open-label extension** (OLE) study for patients who were continuing esketamine NS treatment, following ESCAPE-TRD.

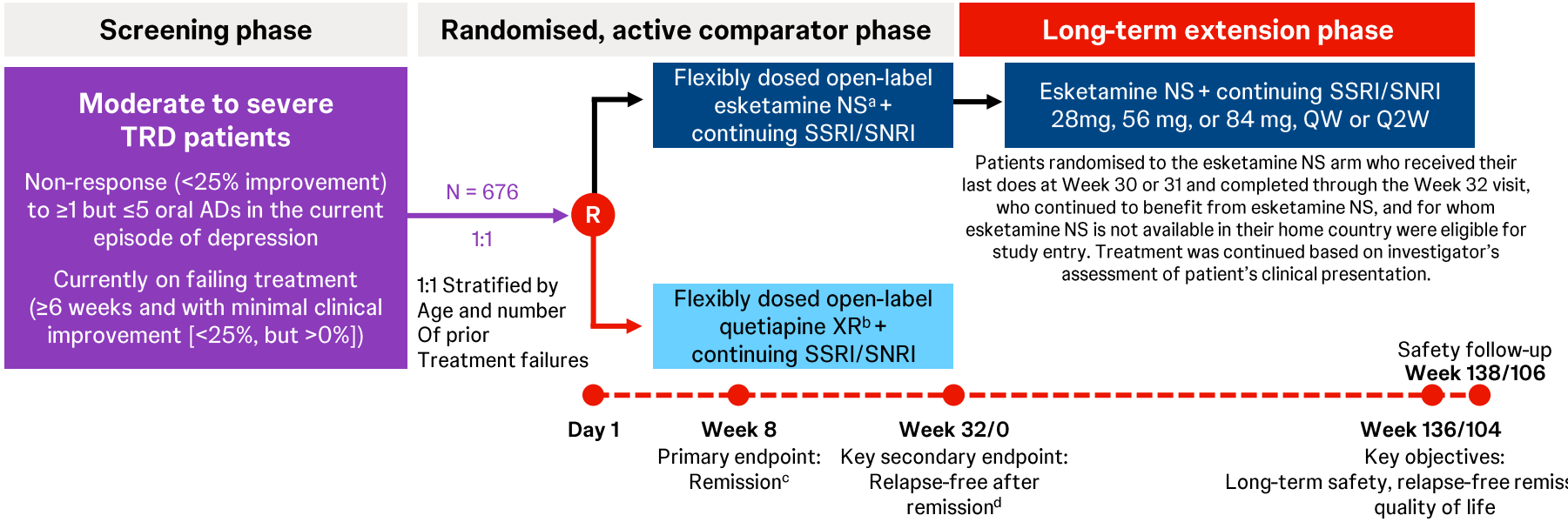
**Objective:** To assess the **long-term safety, tolerability and efficacy of esketamine NS** alongside an SSRI/SNRI in patients with TRD. Here, we report top-line safety and efficacy results from ESCAPE-LTE and ESCAPE-TRD together.

[1]Reif A, et al. NEJM 2023;389:1298–309. NS: nasal spray; OLE: open-label extension; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor;TRD: treatment resistant depression; XR: extended release.

# Methods (1/2)

## Study Design and Treatment

- ESCAPE-LTE was a **single-arm, 2-year OLE to ESCAPE-TRD** in 14 countries. Patients who completed esketamine NS treatment in combination with an SSRI/SNRI to Week 32 in ESCAPE-TRD were eligible for ESCAPE-LTE.
- Esketamine NS starting dose and frequency was determined by the patient's treatment regimen at Week 32 of ESCAPE-TRD.[1] Investigators were able to change the dose and frequency within label recommendations based on clinical judgment. Patients who enrolled continued to receive weekly or biweekly doses of esketamine NS + SSRI/SNRI.




[a]Esketamine NS was flexibly dosed twice weekly from Weeks 1–4, weekly (QW) from Weeks 5–8 and weekly or every two weeks (Q2W) from Weeks 9–32; [b]Quetiapine XR was flexibly dosed and administered daily; [c]Defined as MADRS total score ≤10, no treatment or study discontinuation before Week 8; [d]Defined as MADRS score <22 or no psychiatric hospitalisation or suicide attempt, following MADRS score ≤10 at Week 8.

1. European Medicines Agency. SPRAVATO® (esketamine NS) Summary of Product Characteristics. 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf. Last accessed April 2024. AD: antidepressant; NS: nasal spray; MADRS: Montgomery–Åsberg Depression Rating Scale; OLE: open-label extension; QW: every week; Q2W: every 2 weeks; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment resistant depression; XR: extended release.

# Methods (2/2)

## Outcomes and Statistical Analysis

- One of the primary objectives was to **assess treatment-emergent adverse events** (TEAEs).
- The secondary objectives included the proportion of patients who were **relapse-free to Week 136** and change from baseline in ESCAPE-TRD in the **Montgomery-Åsberg Depression Rating Scale** (MADRS) to Week 136.
- **Relapse was defined by MADRS total score ≥22** at 2 consecutive assessments within 5 to 31 days of each other, hospitalisation for worsening depression, suicide prevention, or suicide attempt, or any other event assessed as indicative of relapse.
- The safety/efficacy analysis set comprised all participants who received at least 1 dose of study treatment during ESCAPE-LTE.
- **Safety data** were analysed from the safety analysis set using data pooled from ESCAPE-TRD and ESCAPE-LTE (Week 0–138 [including safety follow-up]), and from ESCAPE-LTE alone (Week 32–138).
- **Efficacy data** were analysed from the efficacy analysis set, across ESCAPE-TRD and ESCAPE-LTE (Week 0–136) and reported as observed case (OC).
- The proportion of patients with a TEAE and the proportion without relapse or treatment discontinuation were estimated with a 95% Clopper-Pearson confidence interval (CI).

CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; NS: nasal spray; OC: observed case; TEAE: treatment-emergent adverse event.

# Results (1/4)

## Baseline Characteristics

- Baseline characteristics are reported from baseline of ESCAPE-TRD for the 183 patients who enrolled in ESCAPE-LTE.

| Mean (SD), unless otherwise specified | ESCAPE-LTE alone<br>Esketamine NS + SSRI/SNRI<br>(N = 183) |
|---|---|
| Age, years | 44.6 (13.1) |
| Sex, female, n (%) | 128 (69.9) |
| Total treatment failures, n (%)<br>2<br>≥3 | <br>125 (68.3)<br>58 (31.7) |
| Age at MDD diagnosis (years) | 34.5 (11.2) |
| Baseline MADRS total score | 31.5 (5.6) |
| Duration of current episode (weeks) | 52.4 (51.9) |

Baseline characteristics presented from first visit of ESCAPE-TRD, for the safety analysis set of ESCAPE-LTE only (patients who received ≥1 dose of study treatment). MDD: major depressive disorder; MADRS: Montgomery-Åsberg Depression Rating Scale; NS: nasal spray; SD: standard deviation; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

# Results (2/4)

## Safety

- TEAEs were observed in 161 (88.0%) patients in ESCAPE-LTE alone and 177 (96.7%) patients over the course of both ESCAPE-TRD and ESCAPE-LTE, of which 128 (70.0%) and 163 (89.1%) experienced a TEAE possibly related to treatment, respectively.
- **Low proportions of patients experienced serious TEAEs** (ESCAPE-LTE: 6.0%; ESCAPE-TRD/ESCAPE-LTE: 8.2%) or TEAEs leading to treatment discontinuation; one patient experienced a TEAE that resulted in death.
- Over the course of both ESCAPE-TRD and ESCAPE-LTE, the most common TEAEs included **headaches, dizziness and nausea**.
- In ESCAPE-LTE alone and over the course of ESCAPE-TRD and ESCAPE-LTE, almost all TEAEs that occurred on dosing days **resolved on the same day**.

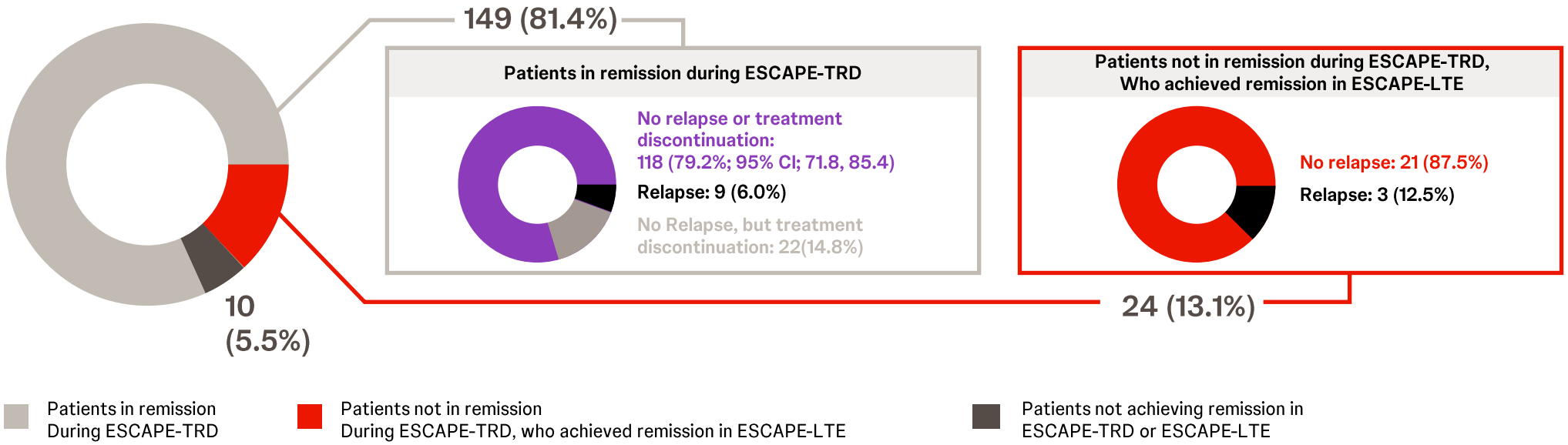
| **Patients experiencing TEAEs, n (% [95% CI])** | **ESCAPE-LTE alone Esketamine NS + SSRI/SNRI (N=183)** | **Pooled ESCAPE-LTE and ESCAPE-TRD Esketamine NS + SSRI/SNRI (N=183)** |
|---|---|---|
| All TEAEs | 161 (88.0 [82.4, 92.3]) | 177 (96.7 [93.0, 98.8]) |
| TEAEs possibly related to study drug | 128 (70.0 [62.7, 76.5]) | 163 (89.1 [83.6, 93.2]) |
| TEAEs leading to death[a] | 1 (0.6 [0.0, 3.0]) | 1 (0.6 [0.0, 3.0])[b] |
| ≥1 serious TEAE | 11 (6.0 [3.0, 10.5]) | 15 (8.2 [4.7, 13.2]) |
| TEAE leading to study drug withdrawal | 6 (3.3 [1.2, 7.0]) | 6 (3.3 [1.2, 7.0])[b] |
| TEAEs leading to dose interruption or modification | 24 (13.1 [8.6, 18.9]) | 37 (20.2 [14.7, 26.8]) |
| **Most frequent TEAEs,** n (%) | | |
| Headache | 81 (44.3) | 95 (51.9) |
| Dizziness | 50 (27.3) | 89 (48.6) |
| Nausea | 37 (20.2) | 74 (40.4) |
| Vertigo | 32 (17.5) | 48 (26.2) |
| Dissociation | 19 (10.4) | 43 (23.5) |
| Nasopharyngitis | 37 (20.2) | 40 (21.9) |
| COVID-19 infection | 30 (16.4) | 39 (21.3) |

Safety data presented for the safety analysis set of ESCAPE-LTE (patients who received ≥1 dose of study treatment). An adverse event was counted as treatment emergent if it started after taking first dose and on or before 14 days after last dose of study medication (the safety follow-up visit). A serious adverse event was counted as treatment emergent if it started within 30 days of the last dose of study medication. [a]One patient experienced a TEAE leading to death as a result of multiple injuries that were unrelated to the study treatment; [b]By design, all deaths/withdrawals reported here happened in ESCAPE-LTE, since the analysis only includes patients who entered the LTE. CI: confidence interval; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TEAE: treatment-emergent adverse event.

# Results (3/4)

## Efficacy - Remission and Relapse

- Of the 149 patients who experienced remission during ESCAPE-TRD, 118 (79.2%) patients did not relapse or discontinue study treatment, and 9 (6.0%) patients experienced relapse, from point of remission and throughout ESCAPE-LTE.
- A total of **24 patients experienced remission during ESCAPE-LTE**, but not in ESCAPE-TRD. The average time to remission was **60.2 weeks** from start of treatment. Of these patients, 3 (12.5%) experienced relapse.
  - The **overall relapse rate** across both studies was **6.9%**.

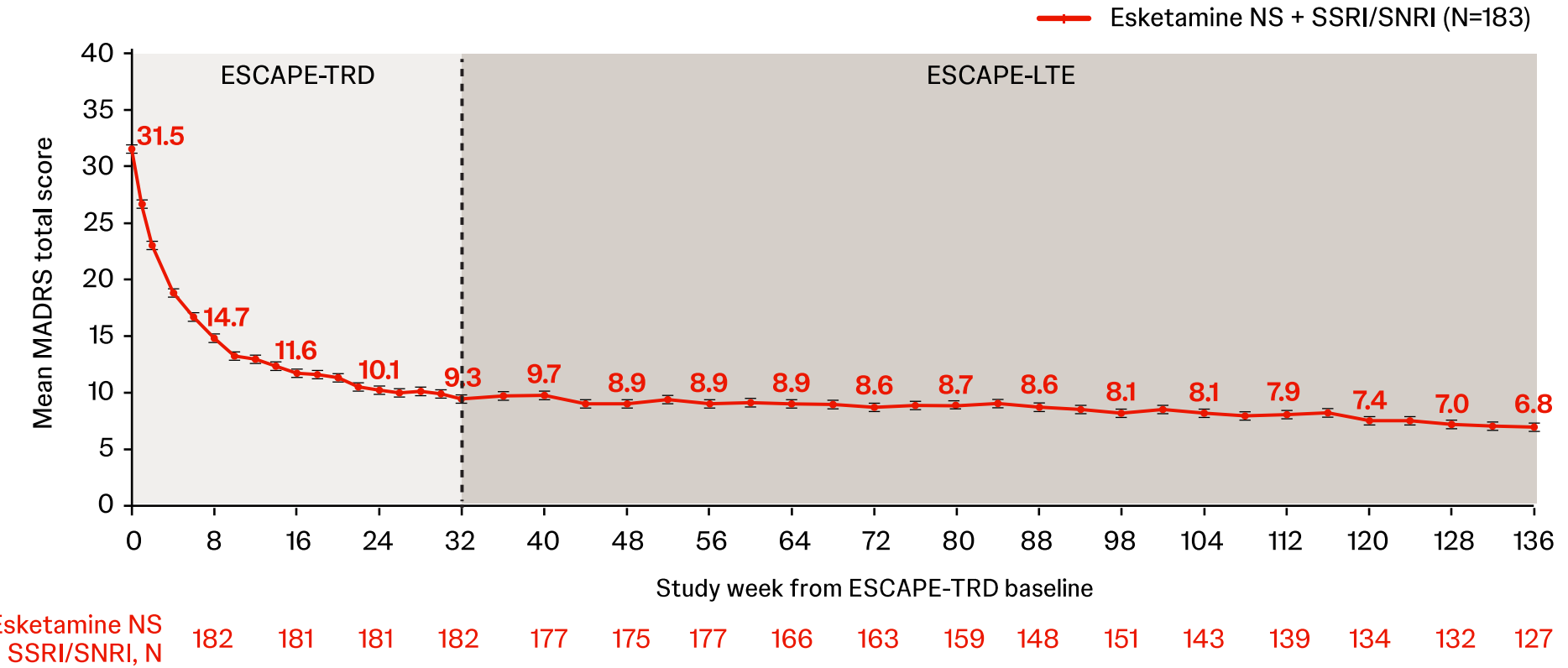



Remission and relapse presented for patients in the efficacy set (patients who received ≥1 dose of study treatment). CI: confidence intervals.

# Results (4/4)

## Efficacy - MADRS Over Time

- Patients showed **rapid reductions** in mean (SE) MADRS score from 31.5 (0.4) at baseline to 14.7 (0.6) at Week 8, and continuous improvements over the long term to 6.8 (0.5) at Week 136.




Mean (±standard error [SE]) MADRS total score presented for patients in the efficacy set (patients who received ≥1 dose of study treatment; observed case). MADRS score ranges from 0 to 60; higher scores indicate a more severe condition.
MADRS: Montgomery-Åsberg Depression Rating Scale; NS: nasal spray; SE: standard error; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

# Conclusion

- Long-term treatment with esketamine NS presented **no new safety concerns** and demonstrated a safety profile consistent with previous results over shorter time periods.[1]
- Low proportions of patients treated with esketamine NS experienced serious TEAEs and **TEAEs rarely led to treatment discontinuation** or interruption.
- **Efficacy outcomes were maintained for most patients over 136 weeks** in ESCAPE-TRD and ESCAPE-LTE with **low relapse rates over the long term** and continuous improvements in mean MADRS score observed over time.

[1]McIntyre RS, et al. Eur Neuropsychopharmacol. 2024;85:58–65. MADRS: Montgomery-Åsberg Depression Rating Scale; NS: nasal spray; TEAE: treatment-emergent adverse event; TRD: treatment resistant depression.