# Esketamine Nasal Spray Versus Quetiapine for Treatment-Resistant Depression

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## Background

- Treatment-resistant depression (TRD) is often defined as occurring when individuals do not respond to 2 or more consecutive treatments with adequate duration and dosage in the current depressive episode[1]
- The randomized, open-label, rater-blinded, long-term, phase 3b ESCAPE-TRD trial compares safety and efficacy outcomes among adults receiving flexible doses of esketamine nasal spray (ESK) and extended-release (XR) quetiapine, both in combination with ongoing treatment with oral antidepressants (OAD)
- A previous publication and subgroup analysis that reported efficacy results from the ESCAPE-TRD trial defined remission as a score of ≤10 on the Montgomery–Åsberg Depression Rating Scale (MADRS) and found that significantly more adults receiving ESK plus OAD achieved remission at week 8, had no relapse through week 32 after remission at week 8, and responded to treatment compared to those receiving quetiapine XR plus OAD[2,3]
  - Although MADRS is a clinician-rated instrument, the 9-item Patient Health Questionnaire (PHQ-9) is a widely used patient-reported outcome that measures the severity of depression, thus complementing previous results by providing participants' experience of their disease and treatment outcomes
- Another previous analysis of participants enrolled in the ESCAPE-TRD trial evaluated efficacy outcomes with PHQ-9, where remission was defined as a PHQ-9 score ≤9 and response was defined as a 50% improvement from baseline in PHQ-9 score or a PHQ-9 score ≤9. This study found that ESK significantly increased the proportion of participants achieving remission/response and shortened time to achieving remission/response[4]
  - However, the population studied and the definitions of response and remission considered in this study were broader than in the US-based prescribing guidelines.[5,6] Therefore, findings may not be directly applicable to U.S.-based populations
  - Given that this analysis focuses on the subgroup of participants treated in accordance with the U.S. prescribing label, a PHQ-9 score <5 instead of PHQ-9 score ≤9 was used to define remission/response[6]

## Objective

- Describe the efficacy, as measured by PHQ-9, for adults with TRD enrolled in the ESCAPE-TRD trial who received ESK plus OAD in accordance with the U.S. prescribing information ("U.S. label subgroup") compared with those treated with quetiapine XR plus OAD

## Methods

- ESCAPE-TRD trial design was described in detail in previous studies evaluating efficacy outcomes among participants receiving ESK and participants receiving quetiapine XR[2-4]
- Outcomes of interest in this subgroup analysis include remission and response at weeks 8 and 32, time to first remission, time to first response, time to confirmed remission, time to confirmed response, and mean change in PHQ-9 score from baseline to week 32
  - Depression severity was defined using PHQ-9 (scores range from 0 to 27, with higher scores indicating more severe depression) and analyzed using the nonresponder imputation approach, whereby individuals discontinuing study treatment without having reached remission/response were assumed to never reach remission/response
    - Adjusted odds ratios (OR), relative risk (RR), and risk difference (RD) with 95% confidence intervals (CI) were estimated using Cochran-Mantel-Haenszel chi-square tests adjusted for number of prior failed treatments (2 versus 3 or more)
    - Remission was defined as PHQ-9 score of <5 and response was defined as a 50% improvement in PHQ-9 score from baseline or a PHQ-9 score of <5
- The PHQ-9 scoring threshold for remission and response was defined as <5 to provide a more conservative definition of these efficacy outcomes and to align with U.S.-based clinical guidelines[6]
  - Median time to first remission/response (first point in time where remission/response is observed) and median time to confirmed remission/response (first point in time where response/remission is observed in 2 consecutive visits) were estimated using the Kaplan-Meier method, and hazard ratios (HR) and 95% CI were estimated using an adjusted Cox proportional hazards model that also adjusted for prior treatment failures.[4] In both analyses, patients discontinuing study treatment were censored at an arbitrarily large time (larger than study duration), i.e., assumed to reach the event
  - Change from baseline in PHQ-9 score during the treatment period was imputed with last-observation-carried-forward (LOCF). Difference in least-square (LS) means, 95% CI, and 2-sided p-value were based on an analysis of covariance (ANCOVA) model with treatment, age group, number of treatment failures, and baseline value as covariates
- Participants discontinuing study treatment without having reached response/remission were assumed to never achieve response/remission for all analyses except for mean change in PHQ-9 score from baseline (imputed LOCF)

## Results

- Among 676 participants in the full population of ESCAPE-TRD, 636 participants were included in this subgroup analysis. 316 participants were assigned to receive ESK and 320 were assigned to receive quetiapine XR. Baseline characteristics of participants included in this subgroup analysis are shown in **Table 1**[3]

**TABLE 1: Baseline characteristics of U.S. label subgroup population in ESCAPE-TRD**

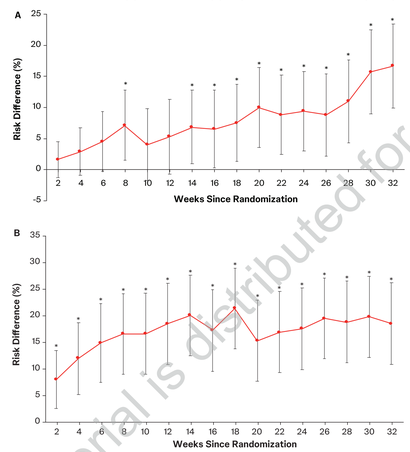
| | ESK N = 316 | Quetiapine XR N = 320 |
|---|---|---|
| Mean age (SD), years | 42.8 (12.56) | 44.5 (12.40) |
| Female, n (%) | 212 (67.1) | 207 (64.7) |
| Race,[a] n (%) | | |
| White | 131 (91.0) | 144 (89.4) |
| Black or African American | 4 (2.8) | 6 (3.7) |
| Asian | 9 (6.3) | 10 (6.2) |
| BMI, kg/m$^2$, n (%) | | |
| Underweight (<18.5) | 6 (2.3) | 5 (1.9) |
| Normal (18.5 to <25) | 105 (39.9) | 84 (31.1) |
| Overweight (25 to <30) | 91 (34.6) | 93 (34.4) |
| Obese (≥30) | 61 (23.2) | 88 (32.6) |
| Number of treatment failures, n (%) | | |
| 2 | 187 (59.2) | 192 (60.0) |
| ≥3 | 129 (40.8) | 128 (40.0) |
| Age when diagnosed with MDD, mean (SD), years | 33.0 (11.58) | 34.4 (11.67) |
| Total number of depressive episodes, mean (SD) | 3.4 (2.42) | 3.5 (4.17) |
| Duration of current episode, mean (SD), weeks | 68.2 (85.28) | 63.2 (62.41) |
| PHQ-9 total score at baseline, mean (SD) | 17.9 (4.3) | 17.4 (4.6) |
| MADRS total score at baseline, mean (SD) | 31.6 (6.08) | 31.1 (5.94) |
| CGI-S total score at baseline, mean (SD) | 4.9 (0.62) | 4.9 (0.71) |

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; PHQ-9: 9-Item Patient Health Questionnaire; XR, extended release.

[a]Collected only for participants who provided biomarker samples.

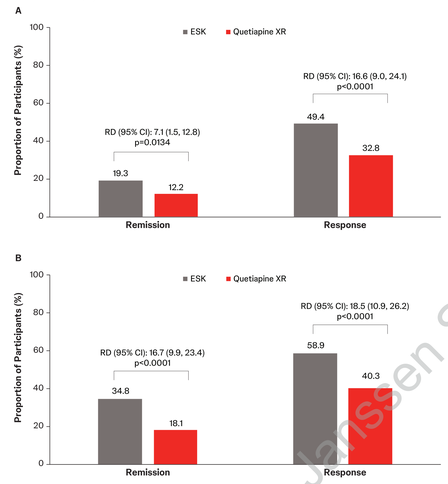
- Although the proportion of participants who achieved remission and response increased over time for both arms, a higher percentage of participants receiving ESK achieved remission and response at weeks 8 and 32 compared to participants receiving quetiapine XR (**Figure 1**). Proportions of patients achieving remission and response at weeks 8 and 32 are shown in **Figures 2A** and **2B**, respectively, below
  - At 8 weeks, 19.3% of participants receiving ESK achieved remission compared to 12.2% of participants receiving quetiapine XR (RD [95% CI]: 7.1% [1.5%, 12.8%]; p = 0.0134). At 32 weeks, 34.8% of participants receiving ESK achieved remission compared to 18.1% of participants receiving quetiapine XR (RD [95% CI]: 16.7% [9.9%, 23.4%]; p < 0.0001)
  - At 8 weeks, 49.4% of participants receiving ESK achieved response compared to 32.8% of participants receiving quetiapine XR (RD [95% CI]: 16.6% [9.0%, 24.1%]; p < 0.0001). At 32 weeks, 58.9% of participants receiving ESK achieved response compared to 40.3% of participants receiving quetiapine XR (RD [95% CI]: 18.5% [10.9%, 26.2%]; p < 0.0001)

**FIGURE 1: Risk difference of (A) remission and (B) response between ESK and quetiapine XR**




ESK, esketamine nasal spray; XR, extended release.

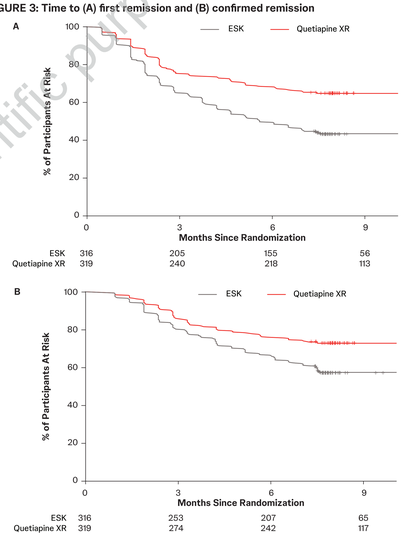
**FIGURE 2: Proportion of participants who achieved remission and response at (A) week 8 and (B) week 32**




CI, confidence interval; ESK, esketamine nasal spray; RD, risk difference; XR, extended release.

- Participants receiving ESK were able to achieve first remission (HR: 1.9; p < 0.0001), first response (HR: 1.7; p < 0.0001), confirmed remission (HR: 1.7; p < 0.0001), and confirmed response (HR: 1.7; p < 0.0001) in less time compared with participants receiving quetiapine XR. Times to first remission and confirmed remission are shown in **Figures 3A** and **3B**, respectively, below. Times to first response and confirmed response are shown in **Figures 4A** and **4B**, respectively, below

**FIGURE 3: Time to (A) first remission and (B) confirmed remission**



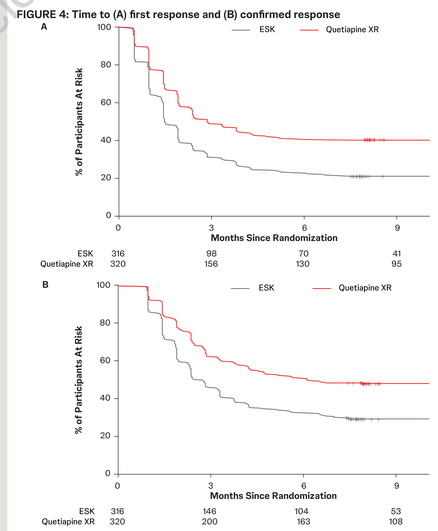

ESK, esketamine nasal spray; XR, extended release.

**TABLE 2: Summary of estimated risk difference at week 8 and week 32 for remission and response**

| | ESK N = 316 | Quetiapine XR N = 320 |
|---|---|---|
| Remission at week 8, n (%) | 61 (19.3) | 39 (12.2) |
| Risk difference (95% CI) | 7.1 | |
| *p* value | p=0.0134 | |
| Response at week 8, n (%) | 156 (49.4) | 105 (32.8) |
| Risk difference (95% CI) | 16.6 | |
| *p* value | p<0.0001 | |
| Remission at week 32, n (%) | 110 (34.8) | 58 (18.1) |
| Risk difference (95% CI) | 16.7 | |
| *p* value | p<0.0001 | |
| Response at week 32, n (%) | 186 (58.9) | 129 (40.3) |
| Risk difference (95% CI) | 18.5 | |
| *p* value | p<0.0001 | |

CI, confidence interval; ESK, esketamine nasal spray; XR, extended release.

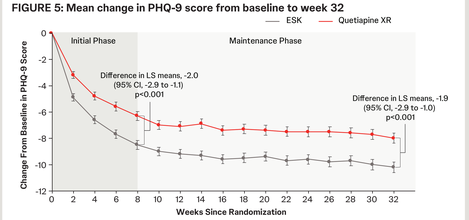
**FIGURE 4: Time to (A) first response and (B) confirmed response**




ESK, esketamine nasal spray; XR, extended release.

- Patients receiving ESK experienced a significantly greater mean change from baseline to 32 weeks in PHQ-9 score (−10.2 vs. −8.0; difference of LS means [95% CI]: −1.9 [−2.9, −1.0]; p < 0.001), indicating greater improvement in depression severity compared with participants receiving quetiapine XR. Mean changes in PHQ-9 score from baseline to 32 weeks are shown in **Figure 5** below

**FIGURE 5: Mean change in PHQ-9 score from baseline to week 32**




CI, confidence interval; LS, least-square.

## Limitations

Limitations in the ESCAPE-TRD trial design comparing esketamine nasal spray and quetiapine extended-release were previously described[2]

- Differences in treatment adherence and route of administration between esketamine nasal spray and quetiapine extended-release may bias the results
- While we restricted this analysis to participants receiving treatment in line with the U.S. prescribing label, there were no U.S. participants included in the study. We therefore assume that the results and conclusions of this subgroup analysis would be transferable to a U.S. population

## Conclusions

Our results show that esketamine nasal spray significantly increased the proportion of participants achieving remission and response in 8 and 32 weeks and shortened time to PHQ-9 remission and response at weeks 8 and 32 with greater improvement in PHQ-9 score from baseline compared to quetiapine extended-release

Esketamine nasal spray exhibited better short- and long-term efficacy per an outcome reported from participants' perspectives on their own disease severity. These results complement and remain consistent with previous studies evaluating the effects of esketamine nasal spray compared to quetiapine extended-release

### Disclosures

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