Variables Associated With Remission in Patients Treated With Esketamine Nasal Spray or Quetiapine Extended-Release: A Post Hoc Subgroup Analysis of the ESCAPE-TRD Study

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Introduction

- Approximately 30% of patients with major depressive disorder (MDD) do not achieve remission despite adherence to adequate treatment with ≥2 oral antidepressants (OADs) and are considered to have treatment-resistant depression (TRD)[1,2]
- Esketamine nasal spray (ESK) is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist approved by the US Food and Drug Administration for use in combination with an OAD for the treatment of adults with TRD[3,4]
- Quetiapine extended-release (QUE XR) is an atypical antipsychotic indicated for the treatment of MDD as an adjunctive therapy with OADs[5]
- ESCAPE-TRD (NCT04338321) was a randomized, open-label, rater-blinded, long-term phase 3b trial comparing ESK versus QUE XR in patients with TRD; patients received either ESK or QUE XR, both in combination with ongoing treatment with an OAD[6]
  - The original study endpoints of remission rate at week 8 and relapse-free rate during the consecutive 24 weeks until week 32, after achieving remission at week 8, were met, thus demonstrating the benefit of ESK versus QUE XR[6]

Objective

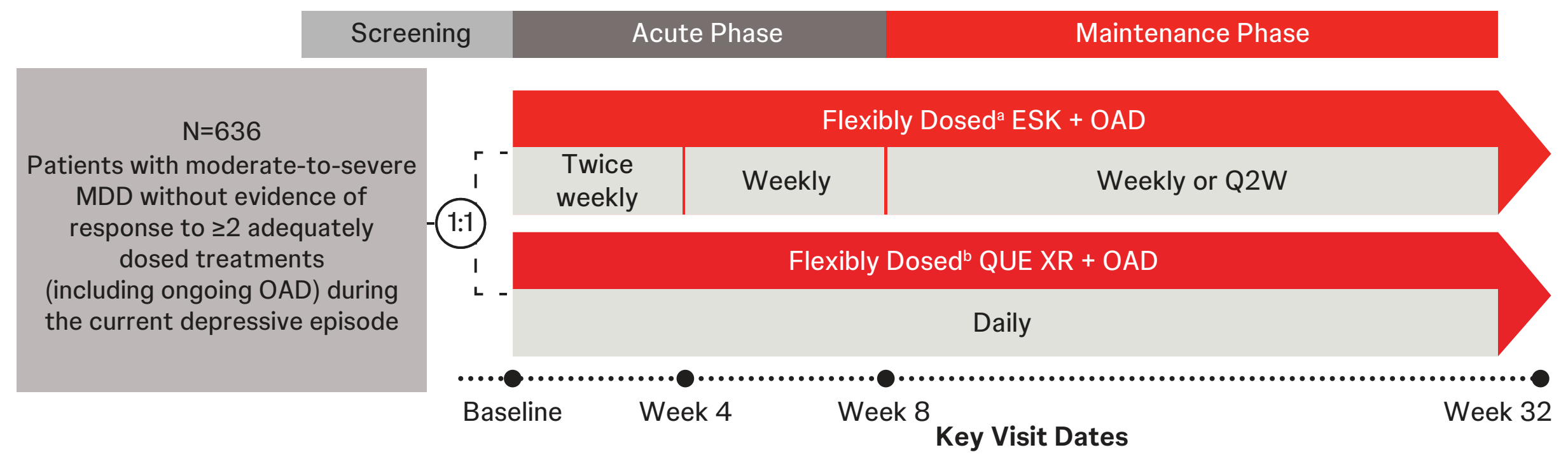
- To examine the baseline and disease characteristics of patients with TRD who achieved remission at week 8 of treatment with ESK or QUE XR (both with an OAD) in ESCAPE-TRD to identify potential variables associated with remission

Methods

Study design

- Data for this exploratory post hoc subgroup analysis were taken from the ESCAPE-TRD trial **(Figure 1)**

FIGURE 1. Study design



ESK, esketamine nasal spray; MDD, major depressive disorder; OAD, oral antidepressant; Q2W, every 2 weeks; QUE XR, quetiapine extended release

[a]ESK was dosed twice weekly (56 mg on day 1 and may be increased to 84 mg from day 4) during weeks 1 to 4, weekly (56 or 84 mg) during weeks 5 to 8, and weekly or Q2W (56 or 84 mg) during weeks 9 to 32, all in addition to ongoing treatment with an OAD.

[b]QUE XR was dosed once daily, starting at 50 mg and titrating up to ≥150 mg/day by the end of week 2 and then flexibly dosed (150 to 300 mg/day) from weeks 3 to 32, all in addition to ongoing treatment with an OAD.

Participants

- Patients were included in the current analysis if they were enrolled in ESCAPE-TRD and received ESK treatment or QUE XR treatment (both consistent with US prescribing information)

Outcome measures and statistical methods

- Key baseline characteristics examined were age, sex, race, ethnicity, weight, height, body mass index (BMI), employment status, region, systolic and diastolic blood pressure, and heart rate
- Key baseline disease characteristics examined were OAD category, number of treatment failures (2 vs ≥3), Montgomery–Åsberg Depression Rating Scale (MADRS) total score, age at MDD diagnosis, screening Clinical Global Impressions Scale (CGI-S) score, duration of current episode, and family history of psychiatric disorders
- Remission was assessed at week 8 and defined as a MADRS total score ≤12
  - In the primary analysis of the ESCAPE-TRD trial, remission was defined as MADRS total score <10; 27.1% of patients in the ESK group had remission at week 8 versus 17.6% in the QUE XR group (*P*=0.003)[6]
- Initial univariate logistic regression models identified demographic or clinical characteristics associated with remission. Significance was defined as *P*<0.05. No adjustment was made for multiplicity
- Stepwise multiple logistic regression models were fit to examine results of the initial models
  - Variables were entered sequentially, at which point variables that became nonsignificant were checked and removed from the model (model parameters: entry *P*≤0.2 and stay *P*≤0.2)
  - Remission rate differences between ESK and QUE XR (observed cases) were evaluated at week 8 using odds ratios (ORs) and corresponding CIs

Results

- Baseline demographics and disease characteristics of patients in the ESCAPE-TRD trial are shown in **Table 1**
  - Median age in the ESK and QUE XR groups was 44.0 and 46.0 years and 67.1% and 64.7% of patients were female, respectively
  - Baseline demographics and disease characteristics were similar between both treatment groups

TABLE 1: Baseline demographics and disease characteristics in ESCAPE-TRD

	ESK N=316	QUE XR N=320
Median age (range), years	44.0 (18-64)	46.0 (18-64)
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)
Median baseline weight (range), kg	76.0 (43.4-124.0)	79.9 (41.5-142.5)
Median baseline BMI (range), kg/m^2	25.7 (17.2-39.2)	27.5 (17.6-45.0)
Number of treatment failures, n (%)		
2	187 (59.2)	192 (60.0)
≥3	129 (40.8)	128 (40.0)
Median age when diagnosed with MDD (range), years	32.0 (10-54)	34.5 (10-55)
Median total number of depressive episodes (range)	3.0 (1-21)	3.0 (1-60)
Median duration of current episode (range), weeks	43.0 (12-780)	38.0 (13-449)
Median MADRS total score at baseline (range)	32.0 (6-52)	31.0 (12-51)
Median CGI-S total score at baseline (range)	5.0 (3-7)	5.0 (3-6)
Median screening CGI-S total score (range)	5.0 (3-7)	5.0 (3-7)
Median PHQ-9 total score at baseline (range)	18.0 (4-27)	18.0 (0-27)
Median screening IDS-C30 total score (range)	44.0 (33-68)	44.0 (31-66)
Median IDS-C30 total score at baseline (range)	44.0 (17-66)	45.0 (28-71)
Median systolic blood pressure (range), mm Hg	122.0 (91-153)	122.0 (81-146)
Median diastolic blood pressure (range), mm Hg	79.0 (56-100)	80.0 (52-93)
Employment status, n (%)		
Employed	177 (56.0)	175 (54.7)
Unemployed	138 (43.7)	145 (45.3)
Other	1 (0.3)	0

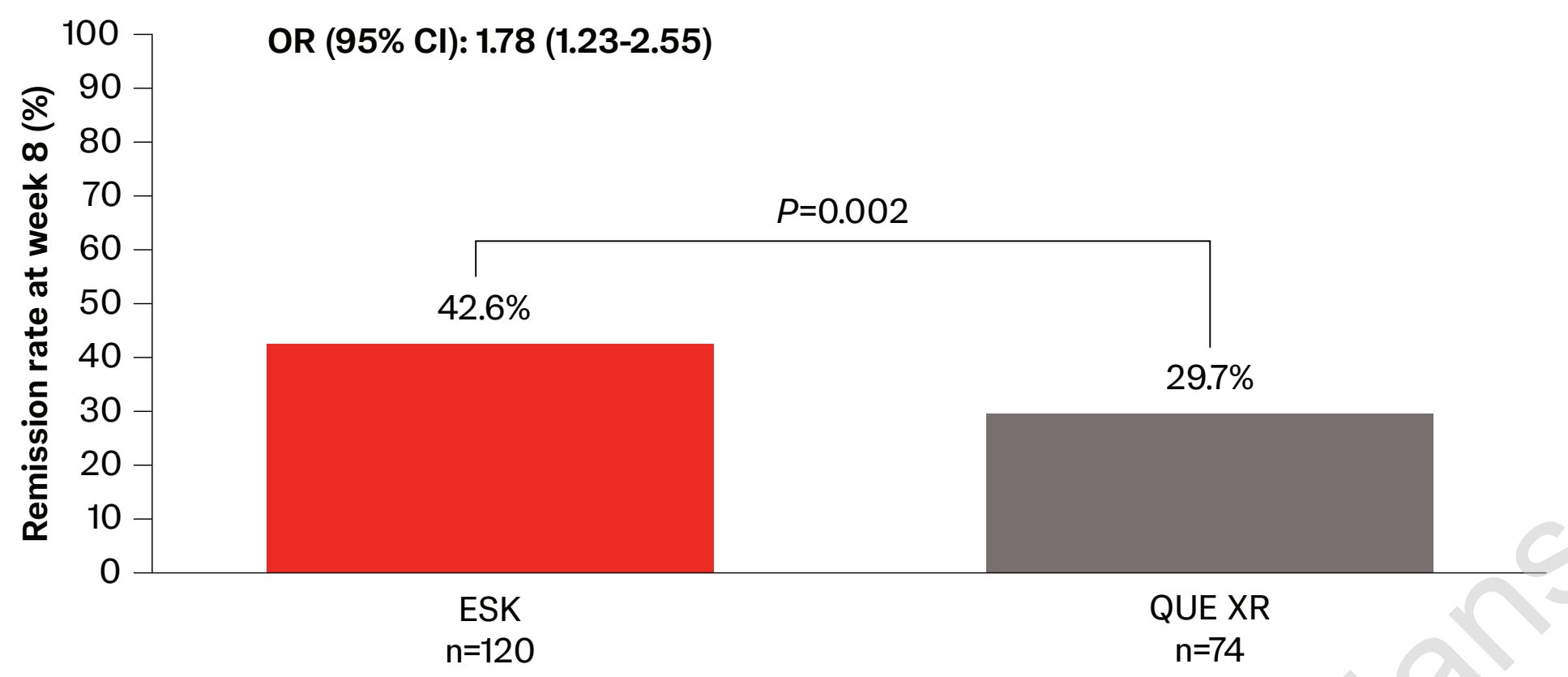
BMI, body mass index; CGI-S, Clinical Global Impressions-Severity scale; ESK, esketamine nasal spray; IDS-C30, 30-item Inventory of Depressive Symptomology, Clinician Rating; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; PHQ-9, 9-item Patient Health Questionnaire; QUE XR, quetiapine extended-release.

[a]Collected for participants who provided biomarker samples.

Remission at week 8

- Remission at week 8 was achieved by 120 of 282 patients (42.6%) treated with ESK and 74 of 249 patients (29.7%) treated with QUE XR **(Figure 2)**
  - Patients treated with ESK had a 78% increase in odds of achieving remission at week 8 (OR: 1.78; 95% CI, 1.23-2.55; *P*=0.002) compared with those treated with QUE XR

FIGURE 2: Remission rates at week 8 with ESK and QUE XR



ESK, esketamine nasal spray; QUE XR, quetiapine extended-release.
Odds ratio, 95% CI, and corresponding *P*-value obtained from logistic regression model adjusted for total number of treatment failures and randomization factor of age.

Univariate analysis of potential variables associated with remission

- Potential variables associated with remission according to univariate logistic models are presented in **Figure 3**
- Based on univariate analysis, in the ESK group, higher baseline weight and BMI, shorter duration of current episode, lower baseline MADRS total score, and lower baseline PHQ-9 total score were identified as potential variables associated with remission
- In the QUE XR group, lower baseline MADRS total score, lower screening and baseline CGI-S score, lower screening and baseline IDS-C30 total score, and fewer prior treatment failures were potential variables associated with remission

FIGURE 3: Variables associated with remission in univariate logistic regression models

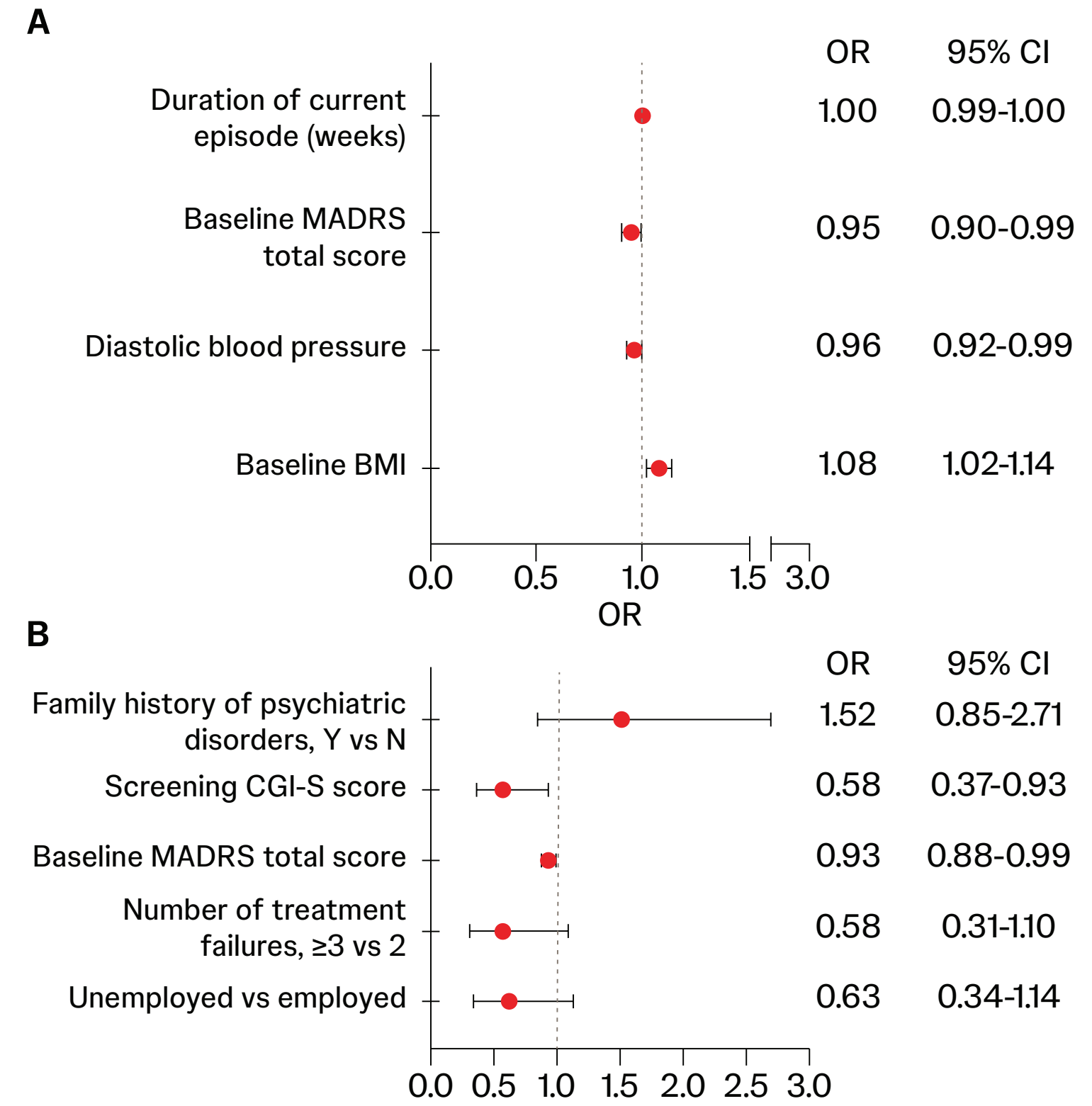
Variable	ESK	QUE XR
Baseline BMI	OR (95% CI): 1.070 (1.015-1.127)	
No. of treatment failures (≥3 vs 2)		OR (95% CI): 0.518 (0.284-0.947)
Duration of current episode (weeks)	OR (95% CI): 0.996 (0.992-1.000)	
Baseline MADRS total score	OR (95% CI): 0.942 (0.903-0.982)	OR (95% CI): 0.905 (0.859-0.954)
Baseline CGI-S score		OR (95% CI): 0.623 (0.421-0.923)
Screening CGI-S score		OR (95% CI): 0.488 (0.319-0.746)
Baseline PHQ-9 total score	OR (95% CI): 0.925 (0.873-0.981)	
Screening IDS-C30 total score		OR (95% CI): 0.938 (0.897-0.980)
Baseline IDS-C30 total score		OR (95% CI): 0.945 (0.905-0.986)

BMI, body mass index; CGI-S, Clinical Global Impressions-Severity Scale; ESK, esketamine nasal spray; MADRS, Montgomery–Åsberg Depression Rating Scale; OR, odds ratio; PHQ-9; 9-item Patient Health Questionnaire; QUE XR, quetiapine extended-release.
Variables with *P*<0.05 in univariate logistical model.
For all continuous variables, each 1-unit increase represents a corresponding change in probability of achieving remission; an OR>1 represents greater odds of achieving remission and an OR<1 represents lower odds.
To convert ORs to probabilities, the following equations are used: if the OR is >1, the equation is OR - 1; if the OR is <1, the equation is 1 - OR. For example, for baseline MADRS total score, the OR for remission in the ESK and QUE XR groups are 0.942 and 0.905, respectively. To convert to probabilities, 1 - OR for ESK and QUE XR are 0.058 (or 5.8%) and 0.095 (or 9.5%), respectively. Therefore, for every point increase in baseline MADRS total score, there is a 5.8% and 9.5% lower log odds of achieving remission in the ESK and QUE XR groups, respectively.

Multivariate analysis of potential variables associated with remission

- Potential variables associated with remission according to stepwise logistic models are presented in **Figure 4**
- Based on multivariate analysis, duration of current episode, baseline MADRS total score, baseline diastolic blood pressure, and baseline BMI were potential variables associated with likelihood of achieving remission in the ESK group
  - Longer duration of current episode (OR 1.00; 95% CI, 0.99-1.00), higher baseline MADRS total score (OR 0.95; 95% CI, 0.90-0.99), and higher baseline diastolic blood pressure (OR 0.96; 95% CI, 0.92-0.99) were associated with lower odds of achieving remission in the ESK group
  - Higher baseline BMI (OR 1.08; 95% CI, 1.02-1.14) was associated with higher odds of achieving remission in the ESK group
- In the QUE XR group, family history of psychiatric disorders, screening CGI-S score, baseline MADRS total score, number of prior treatment failures, and employment status were potential variables associated with likelihood of achieving remission
  - Higher screening CGI-S (OR 0.58; 95% CI, 0.37-0.93), higher baseline MADRS total score (OR 0.93; 95% CI, 0.88-0.99), ≥3 versus 2 prior treatment failures (OR 0.58; 95% CI, 0.31-1.10), and unemployment versus employment (OR 0.63; 95% CI, 0.34-1.14) were associated with lower odds of achieving remission in the QUE XR group
  - Family history of psychiatric disorders (OR 1.52; 95% CI, 0.85-2.71) was associated with higher odds of achieving remission in the QUE XR group

FIGURE 4: Variables associated with remission in stepwise logistic regression models in the (A) ESK group and (B) QUE XR group



BMI, body mass index; CGI-S, Clinical Global Impressions-Severity Scale; MADRS, Montgomery–Asberg Depression Rating Scale; OR, odds ratio; QUE XR, quetiapine extended-release.
Variables with *P*=0.2 entry and *P*=0.2 stay in stepwise logistic model; marginal variables *P*<0.1 in univariate logistic model.
For all continuous variables, each 1-unit increase represents a corresponding change in probability of achieving remission; an OR > 1 represents greater odds of achieving remission and an OR <1 represents lower odds.
To convert ORs to probabilities, the following equations are used: if the OR is >1, the equation is OR - 1; if the OR is <1, the equation is 1 - OR. For example, for baseline MADRS total score, the OR for remission in the ESK and QUE XR groups are 0.95 and 0.93, respectively. To convert to probabilities, 1 - OR for ESK and QUE XR are 0.05 (or 5.0%) and 0.07 (or 7.0%), respectively. Therefore, for every point increase in baseline MADRS total score, there is a 5.0% and 7.0% lower log odds of achieving remission in the ESK and QUE XR groups, respectively.

Remission by baseline demographic and disease characteristics

- For all potential baseline variables associated with remission in either treatment group, the proportion of patients achieving remission at week 8 was higher for patients treated with ESK versus those treated with QUE XR **(Table 2)**
- Across baseline and disease characteristics, the odds of achieving remission at week 8 with ESK were between 1.3 and 3.0 times higher than with QUE XR
  - Baseline MADRS total score higher than the median (OR 3.00; 95% CI, 1.59-5.66), diastolic blood pressure less than or equal to the median (OR 2.39; 95% CI, 1.42-4.03), and screening CGI-S score greater than the median (OR 2.37; 95% CI, 0.72-7.70) were the characteristics associated with the greatest increase in odds of achieving remission at week 8 with ESK versus QUE XR

TABLE 2: Remission rates by baseline demographic and disease characteristics

Baseline characteristic	ESK remission rate, % (n/N)	QUE XR remission rate, % (n/N)	OR (95% CI)
Employment status			
Employed	45.6 (73/160)	34.5 (50/145)	1.60 (1.00-2.53)
Unemployed	38.8 (47/121)	23.1 (24/104)	2.12 (1.18-3.80)
Number of treatment failures			
2	45.6 (77/169)	34.4 (55/160)	1.60 (1.02-2.50)
≥3	38.1 (43/113)	21.3 (19/89)	2.26 (1.20-4.26)
Baseline MADRS total score			
≤Median	50.7 (72/142)	41.1 (58/141)	1.47 (0.92-2.35)
>Median	34.3 (48/140)	14.8 (16/108)	3.00 (1.59-5.66)
Screening CGI-S score			
≤Median	44.9 (110/245)	32.5 (69/212)	1.69 (1.15-2.47)
>Median	27.0 (10/37)	13.5 (5/37)	2.37 (0.72-7.70)
Family history of psychiatric disorders			
Yes	48.8 (62/127)	35.1 (39/111)	1.76 (1.04-2.97)
No	37.4 (58/155)	25.4 (35/138)	1.76 (1.06-2.91)
Baseline BMI			
≤Median	34.5 (41/119)	26.7 (28/105)	1.45 (0.81-2.57)
>Median	50.9 (58/114)	34.3 (36/105)	1.99 (1.15-3.42)
Diastolic blood pressure			
≤Median	44.1 (63/143)	24.8 (31/125)	2.39 (1.42-4.03)
>Median	41.0 (57/139)	34.7 (43/124)	1.31 (0.79-2.16)
Duration of current episode			
≤Median	50.7 (72/142)	33.3 (43/129)	2.06 (1.26-3.37)
>Median	34.3 (48/140)	25.8 (31/120)	1.50 (0.88-2.56)

BMI, body mass index; CGI-S, Clinical Global Impressions-Severity Scale; ESK, esketamine nasal spray; MADRS, Montgomery–Åsberg Depression Rating Scale; OR, odds ratio; QUE XR, quetiapine extended-release.

Limitations

In line with the primary analysis of ESCAPE-TRD, remission rates were assessed at week 8; although 8 weeks may be considered an adequate duration for the evaluation of antidepressant treatment benefit,[7] some patients continued to see treatment benefits beyond week 8, and remission rates may therefore be underrepresented. Using a remission definition of MADRS ≤12, absolute rates of remission at week 32 for ESK and QUE XR were 65.1% and 46.3%, respectively (*P*<0.001)[8]

Variables tested for their association with remission were limited to those collected within the trial

Differences in treatment adherence and routes of administration could potentially introduce bias in the results

A difference in the frequency and duration of study visits between groups is a potential confounder. Because ESK must be administered under the supervision of a healthcare professional, patients in the ESK arm had twice-weekly visits for the first 4 weeks of the study; during the same period, patients in the QUE XR arm had once-weekly visits

Conclusions

✓ In this exploratory post hoc subgroup analysis of patients treated with ESK or QUE XR, according to US prescribing information, ESK was associated with greater odds of achieving remission at week 8 compared to QUE XR; these findings were consistent with the overall ESCAPE-TRD results[6]

✓ Potential variables associated with a higher likelihood of remission in the ESK group were shorter duration of current episode, lower baseline MADRS total score, lower baseline diastolic blood pressure, and higher BMI

✓ In the QUE XR group, potential variables associated with a higher likelihood of remission were family history of psychiatric disorders, lower screening CGI-S score, lower baseline MADRS total score, fewer prior treatment failures, and employment

✓ Although variables associated with remission varied between both treatment groups, patients treated with ESK were more likely to achieve remission at week 8 compared with those treated with QUE XR across all characteristics

✓ Across baseline and disease characteristics, the odds of achieving remission at week 8 with ESK were between 1.3 and 3.0 times higher than with QUE XR

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Disclosures

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