PO-424

Esketamine nasal spray improves rate and time to remission versus quetiapine extended release in subgroups of patients with treatment resistant depression and two or three plus prior treatment failures: Results from ESCAPE-TRD, a randomised phase IIIb trial

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INTRODUCTION

- For patients with major depressive disorder, the likelihood of remission decreases with each subsequent treatment failure.[1]
- Treatment resistant depression (TRD) is commonly defined as non-response to ≥2 consecutive treatments at adequate dosage and duration in the current depressive episode.[2]
- In the ESCAPE-TRD (NCT04338321) phase IIIb trial, esketamine nasal spray (NS) increased the probability of achieving remission at Week 8 and being relapse-free through Week 32 after remission at Week 8 versus quetiapine extended release (XR) in patients with TRD.[3]

OBJECTIVE

- To report the efficacy of esketamine NS versus quetiapine XR in patient subgroups with 2 or ≥3 consecutive prior treatment failures.

METHODS

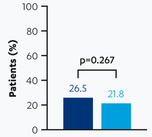
- Patients were randomised 1:1 to esketamine NS or quetiapine XR alongside an ongoing selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (SSRI/SNRI).[4,5]
- Randomisation was stratified by age (18–≤64 years; 65–<75 years) and prior treatment failures (2; ≥3).
- Rates of remission at Week 8 (primary endpoint; Montgomery-Åsberg Depression Rating Scale [MADRS] total score ≤10) and of being relapse-free through Week 32 after remission at Week 8 (key secondary endpoint) were analysed in prior treatment failure patient subgroups and compared between arms. Discontinuation was considered a negative outcome.
- The effect on time to remission for each prior treatment failure subgroup was assessed using hazard ratios (HR) from a Cox regression model. Patients discontinuing treatment were censored at an infinite (arbitrarily large) time and were assumed to never achieve remission.
- Odds ratios (OR), risk ratios (RR) and HR are reported with 95% confidence intervals (CI). P values reported are not adjusted for multiple testing.

RESULTS

- Baseline characteristics, including consecutive prior treatment failures, were consistent between randomisation groups and have been reported previously.[3]
- A greater proportion of patients with 2 prior treatment failures achieved remission at Week 8 with esketamine NS versus quetiapine XR: 26.5% versus 21.8% (OR [95% CI]: 1.291 [0.822, 2.028], p=0.267; RR [95% CI]: 1.214 [0.862, 1.711]; **Figure 1A**).
- Greater proportions of patients with 2 prior treatment failures were relapse-free through Week 32 after remission at Week 8: 24.0% versus 18.0% (OR: 1.439 [0.894, 2.316], p=0.133; RR: 1.334 [0.914, 1.945]; **Figure 1B**).
- A significantly greater proportion of patients with ≥3 prior treatment failures achieved remission at Week 8 with esketamine NS versus quetiapine XR: 28.0% versus 10.9% (OR: 3.199 [1.633, 6.267], p=0.001; RR: 2.583 [1.468, 4.545]; **Figure 2A**).
- Significantly greater proportions of patients with ≥3 prior treatment failures were relapse-free through Week 32 after remission at Week 8 with esketamine NS versus quetiapine XR: 18.2% versus 7.8% (OR: 2.644 [1.209, 5.782], p=0.013; RR: 2.345 [1.169, 4.707]; **Figure 2B**).
- Esketamine NS significantly improved time to remission versus quetiapine XR in both subgroups (2 prior treatment failures HR [95% CI]: 1.547 [1.210, 1.976], **Figure 3**; ≥3 prior treatment failures HR: 2.066 [1.469, 2.907], **Figure 4**).
- The percentage of patients who achieved remission increased over time for patients with 2 (**Figure 5**) and ≥3 prior treatment failures (**Figure 6**) in both treatment arms, and was consistently higher in the esketamine NS arm compared with quetiapine XR.

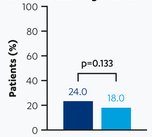
FIGURE 1. Proportion of patients with 2 prior treatment failures achieving primary and key secondary endpoints (NRI)

(A) Primary endpoint – remission at Week 8[a]



	Esketamine NS[b] + SSRI/SNRI N=204	Quetiapine XR[b] + SSRI/SNRI N=211
Primary endpoint Remission at Week 8,[a] n (%)	54 (26.5)	46 (21.8)
Difference in percentage[c] (95% CI)	4.7 (−3.6, 12.9)	
Adjusted OR[c] (95% CI)	1.291 (0.822, 2.028)	
Adjusted p value[d]	0.267	
Adjusted RR[c] (95% CI)	1.214 (0.862, 1.711)	

(B) Key secondary endpoint – remaining relapse-free to Week 32 following remission at Week 8[a]

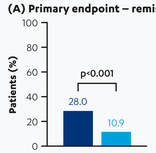


	Esketamine NS[b] + SSRI/SNRI N=204	Quetiapine XR[b] + SSRI/SNRI N=211
Key secondary endpoint Remaining relapse-free to Week 32 following remission at Week 8,[a] n (%)	49 (24.0)	38 (18.0)
Difference in percentage[c] (95% CI)	6.0 (−1.8, 13.8)	
Adjusted OR[c] (95% CI)	1.439 (0.894, 2.316)	
Adjusted p value[d]	0.133	
Adjusted RR[c] (95% CI)	1.334 (0.914, 1.945)	

Full analysis set. [a]Remission was defined as a MADRS total score of ≤10; [b]Esketamine NS and quetiapine XR were both flexibly dosed and taken in addition to an ongoing SSRI/SNRI; [c]Treatment groups were compared using a Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for age group (18–≤64 years; 65–<75 years); [d]Tested at a two-sided 0.05 significance level without adjustment for multiple testing; [e]Patients who discontinued treatment were imputed as non-responders, LOCF was used for patients with missing MADRS assessment at Week 8 who remained in the study.

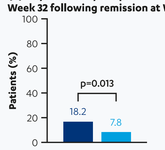
FIGURE 2. Proportion of patients with ≥3 prior treatment failures achieving primary and key secondary endpoints (NRI)

(A) Primary endpoint – remission at Week 8[a]



	Esketamine NS[b] + SSRI/SNRI N=132	Quetiapine XR[b] + SSRI/SNRI N=129
Primary endpoint Remission at Week 8,[a] n (%)	37 (28.0)	14 (10.9)
Difference in percentage[c] (95% CI)	17.2 (7.8, 26.5)	
Adjusted OR[c] (95% CI)	3.199 (1.633, 6.267)	
Adjusted p value[d]	0.001	
Adjusted RR[c] (95% CI)	2.583 (1.468, 4.545)	

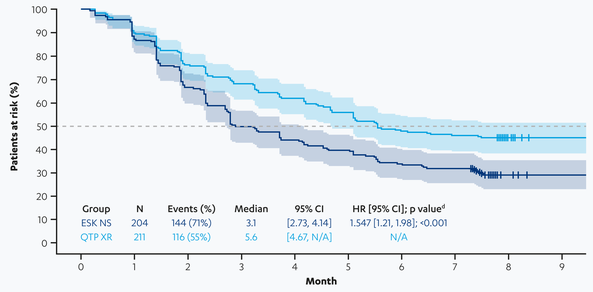
(B) Key secondary endpoint – remaining relapse-free to Week 32 following remission at Week 8[a]



	Esketamine NS[b] + SSRI/SNRI N=132	Quetiapine XR[b] + SSRI/SNRI N=129
Key secondary endpoint Remaining relapse-free to Week 32 following remission at Week 8,[a] n (%)	24 (18.2)	10 (7.8)
Difference in percentage[c] (95% CI)	10.4 (2.4, 18.5)	
Adjusted OR[c] (95% CI)	2.644 (1.209, 5.782)	
Adjusted p value[d]	0.013	
Adjusted RR[c] (95% CI)	2.345 (1.169, 4.707)	

Full analysis set. [a]Remission was defined as a MADRS total score of ≤10; [b]Esketamine NS and quetiapine XR were both flexibly dosed and taken in addition to an ongoing SSRI/SNRI; [c]Treatment groups were compared using a Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for age group (18–≤64 years; 65–<75 years); [d]Tested at a two-sided 0.05 significance level without adjustment for multiple testing; [e]Patients who discontinued treatment were imputed as non-responders, LOCF was used for patients with missing MADRS assessment at Week 8 who remained in the study.

FIGURE 3. Time to remission for patients with 2 prior treatment failures[a–c]

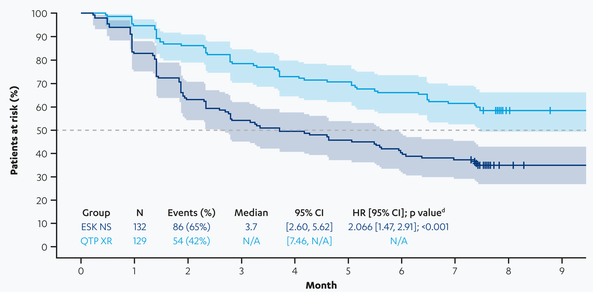


Group	N	Events (%)	Median	95% CI	HR [95% CI]; p value[d]
ESK NS	204	144 (71%)	3.1	[2.73, 4.14]	1.547 [1.21, 1.98]; <0.001
QTP XR	211	116 (55%)	5.6	[4.67, N/A]	N/A

ESK NS	204	178	136	102	90	81	69	65	36	33
QTP XR	211	190	161	144	131	118	101	97	73	66

Full analysis set. [a]Remission was defined as a MADRS total score of ≤10; [b]Patients discontinuing treatment were censored at an infinite (arbitrarily large) time and were assumed to never achieve remission; [c]Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI; [d]Tested at a two-sided 0.05 significance level without adjustment for multiple testing.

FIGURE 4. Time to remission for patients with ≥3 prior treatment failures[a–c]

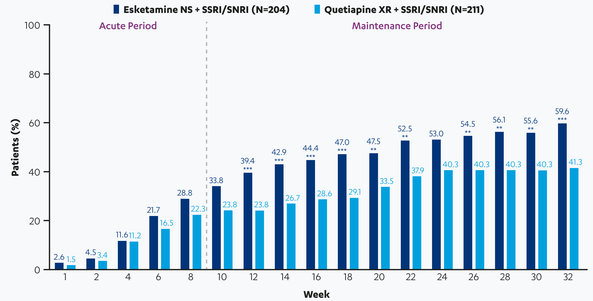


Group	N	Events (%)	Median	95% CI	HR [95% CI]; p value[d]
ESK NS	132	86 (65%)	3.7	[2.60, 5.62]	2.066 [1.47, 2.91]; <0.001
QTP XR	129	54 (42%)	N/A	[7.46, N/A]	N/A

ESK NS	132	109	83	71	65	60	53	49	27	25
QTP XR	129	122	111	101	94	91	85	79	51	49

Full analysis set. [a]Remission was defined as a MADRS total score of ≤10; [b]Patients discontinuing treatment were censored at an infinite (arbitrarily large) time and were assumed to never achieve remission; [c]Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI; [d]Tested at a two-sided 0.05 significance level without adjustment for multiple testing.

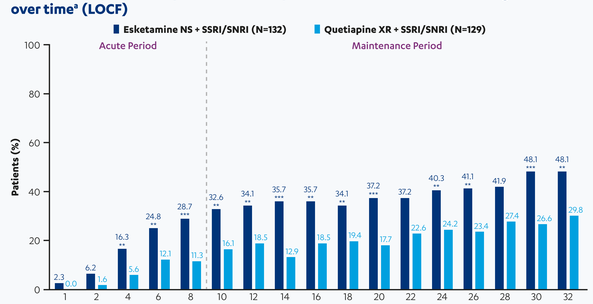
FIGURE 5. Proportion of patients with 2 prior treatment failures achieving remission over time[a] (LOCF)



ESK NS	196	198	198	198	198	198	198	198	198	198	198	198	198	198	198	198	198
QTP XR	205	206	206	206	206	206	206	206	206	206	206	206	206	206	206	206	206

Percentages are based on the number of patients at each timepoint, using LOCF for missing data (on-treatment visits only). Tested at a two-sided 0.05 significance level without adjustment for multiple testing. [a]Remission was defined as a MADRS total score of ≤10. **p<0.01; ***p<0.001.

FIGURE 6. Proportion of patients with ≥3 prior treatment failures achieving remission over time[a] (LOCF)



ESK NS	129	129	129	129	129	129	129	129	129	129	129	129	129	129	129	129	129
QTP XR	121	124	124	124	124	124	124	124	124	124	124	124	124	124	124	124	124

Percentages are based on the number of patients at each timepoint, using LOCF for missing data (on-treatment visits only). Tested at a two-sided 0.05 significance level without adjustment for multiple testing. [a]Remission was defined as a MADRS total score of ≤10. **p<0.01; ***p<0.001.

SUMMARY

- Esketamine NS demonstrated a **superior remission rate** in patients with ≥3 prior treatment failures, with patients **2.6 times as likely** to achieve remission versus quetiapine XR at Week 8.
- Esketamine NS shortened **time to remission** in patients with 2 and ≥3 prior treatment failures, with patients **1.5 and 2.0 times as likely** to achieve remission versus quetiapine XR at any time, respectively.
- These analyses **support the results of the ESCAPE-TRD primary analysis** in the full trial population and demonstrate the efficacy of esketamine NS in patients with both 2 and ≥3 prior treatment failures.

AUTHOR CONTRIBUTIONS: Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **AHY, WJC, REN, AP, TI, SMH, NP, BR, PT, IU, YG**; Drafting of the publication, or revising it critically for important intellectual content: **AHY, WJC, REN, AP, TI, SMH, NP, BR, PT, IU, YG**; Final approval of the publication: **AHY, WJC, REN, AP, TI, SMH, NP, BR, PT, IU, YG**.
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ABBREVIATIONS: CI: confidence internal; **CMH:** Cochran-Mantel-Haenszel; **ESK:** esketamine; **HR:** hazard ratio; **LOCF:** last observation carried forward; **MADRS:** Montgomery-Åsberg Depression Rating Scale; **NA:** not applicable; **NRI:** non-responder imputation; **NS:** nasal spray; **QTP:** quetiapine; **RR:** risk ratio; **SNRI:** serotonin norepinephrine reuptake inhibitor; **SSRI**: selective serotonin reuptake inhibitor; **TRD:** treatment resistant depression; **XR:** extended release.

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