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Efficacy of esketamine nasal spray over quetiapine extended release over the short and long term: sensitivity analyses of ESCAPE-TRD, a randomised phase IIIb clinical trial

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Background

In patients with treatment resistant depression (TRD), the ESCAPE-TRD study showed esketamine nasal spray was superior to quetiapine extended release.

Aims

To determine the robustness of the ESCAPE-TRD results and confirm the superiority of esketamine nasal spray over quetiapine extended release.

Method

ESCAPE-TRD was a randomised, open-label, rater-blinded, active-controlled phase IIIb trial. Patients had TRD (i.e. non-response to two or more antidepressive treatments within a major depressive episode). Patients were randomised 1:1 to flexibly dosed esketamine nasal spray or quetiapine extended release, while continuing an ongoing selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor. The primary end-point was achieving a Montgomery–Åsberg Depression Rating Scale score of ≤10 at Week 8, while the key secondary end-point was remaining relapse free through Week 32 after achieving remission at Week 8. Sensitivity analyses were performed on these end-points by varying the definition of remission based on timepoint, threshold and scale.

Results

Of 676 patients, 336 were randomised to esketamine nasal spray and 340 to quetiapine extended release. All sensitivity analyses on the primary and key secondary end-point favoured esketamine nasal spray over quetiapine extended release, with relative risks ranging from 1.462 to 1.737 and from 1.417 to 1.838, respectively (all $p < 0.05$). Treatment with esketamine nasal spray shortened time to first and confirmed remission (hazard ratio: 1.711 [95% confidence interval 1.402, 2.087], $p < 0.001$; 1.658 [1.337, 2.055], $p < 0.001$).

Conclusion

Esketamine nasal spray consistently demonstrated significant superiority over quetiapine extended release using all pre-specified definitions for remission and relapse. Sensitivity analyses supported the conclusions of the primary ESCAPE-TRD analysis and demonstrated robustness of the results.

Keywords

Esketamine nasal spray; sensitivity analysis; quetiapine extended release; treatment resistant depression; long-term treatment.

Treatment resistant depression (TRD), most commonly defined as non-response to two or more pharmacological treatments of adequate duration and dose within the same major depressive episode (MDE),[1] affects 10–30% of patients with major depressive disorder (MDD).[2] The two key treatment goals for patients with TRD are remission and prevention of relapse.[3,4] Remission is the accepted short-term treatment goal, whilst prevention of relapse is a desired longer-term goal.[5] Remission rates in patients with TRD who require three or more consecutive treatments are lower compared to patients who received fewer prior treatments.[2,6] Therefore, a substantial unmet need exists for short- and long-term treatment of TRD.[7]

There is no one singular guideline-recommended strategy to treat patients with TRD;[7–9] two currently available treatments are quetiapine extended release and esketamine nasal spray. Quetiapine extended release is one of the most commonly used augmentation therapies for TRD, and is approved for patients with MDD who have experienced a sub-optimal response to antidepressant monotherapy.[10–12] Esketamine nasal spray, the only treatment specifically approved for TRD in Europe,[13] has demonstrated a superior reduction of depressive symptoms compared with placebo when both were given in combination with a newly initiated selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI).[14–16]

ESCAPE-TRD was an open-label, rater-blinded, randomised clinical trial that compared flexibly dosed esketamine nasal spray with quetiapine extended release, both in combination with an ongoing SSRI/SNRI, in patients with TRD.[17] It is one of the few existing head-to-head studies in TRD, and was the first head-to-head study comparing esketamine nasal spray with an augmentation strategy. The ESCAPE-TRD study demonstrated the superiority of esketamine nasal spray over quetiapine extended release over short- and long-term treatment periods.[17] Esketamine nasal spray significantly increased the odds of achieving remission at Week 8 (primary end-point), and of being relapse-free through to Week 32 after achieving remission at Week 8 (key secondary end-point).[17]

Determining robustness of results

The primary and key secondary end-points are in line with the treatment goals in the acute and the maintenance periods and represent clinically meaningful outcomes for patients. Achieving the primary end-point requires meeting the treatment goal in the acute period,

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and achieving the key secondary end-point requires meeting the treatment goals in both acute and maintenance periods.

There are no universally accepted definitions for remission or relapse; prior studies in the field have used different timeframes, scales and thresholds.[5,18–20] The definitions chosen for the ESCAPE-TRD study are based on the Montgomery–Åsberg Depression Rating Scale (MADRS). As achieving remission without relapse is a goal for patients,[3,4] examining the robustness of the primary and key secondary outcomes using different definitions of remission and relapse is important and will govern treatment decisions in a TRD treatment plan.

Aim

Here, we explore the robustness of the main findings from the ESCAPE-TRD study through extensive sensitivity analyses. These sensitivity analyses incorporate alternative definitions of the primary and key secondary end-points, as well as additional outcomes such as remission over time and time to remission and response.

Method

Study design and patient inclusion and exclusion criteria

ESCAPE-TRD (NCT04338321) was a randomised, open-label, rater-blinded, active-controlled phase IIIb study that aimed to evaluate the efficacy and safety of esketamine nasal spray versus quetiapine extended release, both flexibly dosed according to their approved labels in combination with a continuing SSRI/SNRI, in patients with TRD. For further details concerning ESCAPE-TRD, please see Supplementary Appendix 1 available at https://doi.org/10.1192/bjp.2024.124 and the previously published full methodology.[17]

The ESCAPE-TRD study was conducted in accordance with the Declaration of Helsinki;[21] country-specific ethics review boards provided approval. All patients provided written informed consent and the study was registered at ClinicalTrials.gov.

Outcomes

Sensitivity analyses of primary and key secondary end-points

The primary end-point, assessing short-term efficacy, was the proportion of patients who achieved remission (defined as a MADRS total score of ≤10)[22] at the Week 8 visit. The key secondary end-point, assessing combined short-and long-term efficacy, was the proportion of patients who were relapse-free through to Week 32 after achieving remission at Week 8. As such, patients were required to satisfy both conditions (remission at Week 8 and no relapse from Week 8 to Week 32) to be considered as having a positive key secondary end-point; any deviation from these conditions (not achieving remission at Week 8 or experiencing relapse between Week 8 and Week 32) was considered a negative key secondary end-point. Outcomes from these end-points have been reported previously.[17]

Relapse was defined as any one of the following: a MADRS score of ≥22 at two consecutive assessments within 5–15 days of each other; admission to hospital for worsening depression, suicide prevention or suicide attempt; suicide attempt; completed suicide or any other clinically relevant event determined by the investigator's clinical judgement. However, throughout the trial, no patients were considered to have relapsed based on this clinical judgement criterion alone.

Sensitivity analyses were pre-specified on the primary and key secondary end-points by varying parameters in their definitions, namely the timepoints, thresholds and scales used. A summary of all sensitivity analyses performed can be found in Supplementary Table 1.

For analyses based on alternative thresholds, the threshold for remission at Week 8 was adjusted to MADRS total scores of ≤8 and ≤12, and the alternative threshold for relapse was adjusted to a MADRS total score of 18 or greater. An additional alternative for relapse used a Clinical Global Impression-Severity scale (CGI-S) score of ≥5 as a threshold for relapse, while keeping all other components of the definition unchanged.

For analyses based on timepoints, the time to achieve remission was changed to Week 6, Week 10 and any point at or before Week 8. The timepoint for relapse was also changed; the key secondary end-point was redefined as relapse from Week 8 to Week 24 (4 months after remission) after remission at Week 8.[5]

Varying parameters related to the primary end-point affected outcomes for the key secondary end-point. For example, when the timepoint for remission was adjusted to Week 6, achieving the 'changed' key secondary end-point would be defined as remission at Week 6 and remaining relapse-free through Week 32. Alternative definitions for the key secondary end-point (i.e. the cut-off for relapse) did not affect the primary end-point. All sensitivity analyses differed from the main analysis by one element only (e.g. timepoint, threshold) to examine independently if this element influenced the result.

Remission rates over time

Rates of remission were estimated over time (all study visits where MADRS score was assessed) using the different remission cut-offs from previous analyses (MADRS ≤8, ≤10, ≤12).

Time to first and confirmed remission and response

Both remission and response were analysed as time to event end-points. Time to first remission was defined as the duration of time elapsed from baseline to the visit at which a patient achieved a MADRS total score of ≤10, and first response was defined as the duration of time until a ≥50% improvement from baseline in MADRS total score, or MADRS ≤10, was reported. Time to confirmed remission and response were defined as the time to the first occurrence of achieving remission or response at two consecutive visits.

Type of MADRS assessment

As the ESCAPE-TRD study was conducted during the coronavirus-19 (COVID-19) pandemic, additional flexibility (e.g. video assessments) had to be permitted to maintain follow-up of patients, and accommodate for the COVID-19 pandemic and related restrictions. An analysis providing an estimation of the impact of COVID-related additional flexibility on the MADRS results can be found in Supplementary Appendix 2.

Statistical analysis

All statistical tests were two-sided based on a significance level of 0.05. No adjustment for multiple testing was implemented.

Binary end-points

The primary and key secondary end-points were analysed using non-responder imputation (NRI), whereby stopping treatment was considered a negative outcome. In addition, missing Week 8 visits for patients still on study treatment were imputed using last observation carried forward (LOCF).

Sensitivity analyses for the primary and key secondary end-points were conducted using the same methodology as those used in the primary publication.[17] Odds ratios, risk differences, relative risks (here the term 'risk' is a generic term referring to the

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probability of experiencing a positive event under analysis, e.g. remission at Week 8) and the number needed to treat (NNT) are reported with 95% confidence intervals (CIs) for each sensitivity analysis, and were derived from Cochran–Mantel–Haenszel chi-square tests adjusted for age (18–≤64 years; 65–≤74 years) and total number of prior treatment failures (2; ≥3).

Rates of remission over time were estimated based on on-treatment visits. Missing data were imputed using NRI or LOCF. Rates were compared using unadjusted relative risks.

Time to event end-points

Time to MADRS remission and response were analysed using the Kaplan–Meier method and study interventions were compared using a two-sided log-rank test for the full analysis set. Time to event parameters such as time to MADRS remission and response were summarised with median, 25th and 75th percentiles (if estimable). Hazard ratios with 95% CIs were estimated using Cox proportional hazard models stratified by age (18–≤64 years; 65–≤74 years) and total number of previous treatment failures (2; ≥3).

Observed data from patients were included in the analyses for as long as patients remained on study intervention (esketamine nasal spray or quetiapine extended release). Patients that dropped out or discontinued study intervention were censored at an 'infinite' time (arbitrarily set at 9999 days) and assumed never to have achieved the event, similar to NRI.

Results

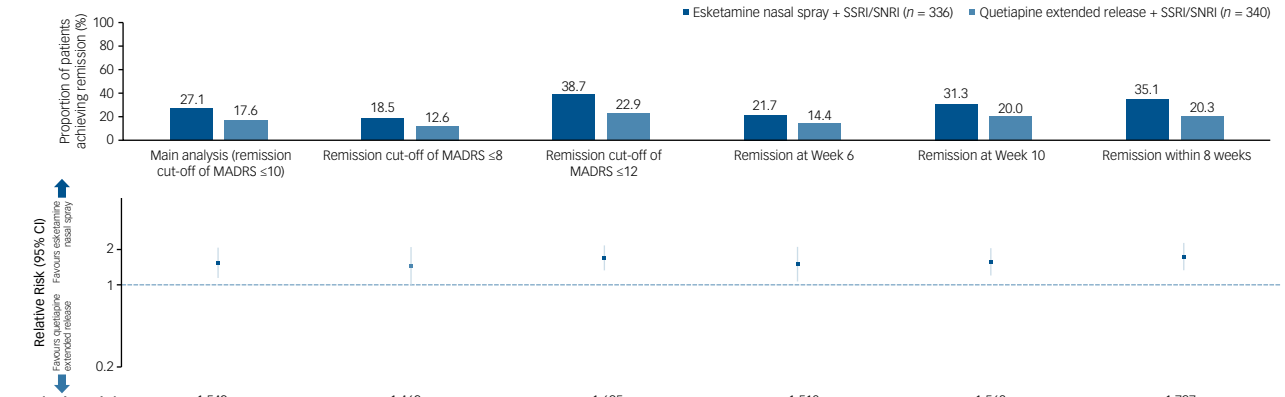
Patient disposition and baseline adjunctive treatment

Of 676 total patients, 336 were randomised to esketamine nasal spray + SSRI/SNRI and 340 were randomised to quetiapine extended release + SSRI/SNRI.[17] Of all randomised patients, 295 and 250 esketamine nasal spray-treated and quetiapine extended release-treated patients completed the acute phase (Week 8), and 258 and 203 patients completed the maintenance phase, respectively. Further details can be found in Supplementary Table 2. Details concerning adjunctive antidepressant treatments at baseline can be found in Supplementary Figure 1.

Sensitivity analyses of the primary and key secondary end-points

All sensitivity analyses on the primary end-point (remission at Week 8) favoured esketamine nasal spray over quetiapine extended release, with relative risks ranging from 1.462 to 1.737 (all $p < 0.05$; Fig. 1). When the remission cut-off was reduced to a MADRS total score of 8, 18.5% (62/336) of esketamine nasal spray-treated patients achieved remission at Week 8 compared with 12.6% (43/340) of quetiapine extended release-treated patients (relative risk [95% CI]: 1.462 [1.017, 2.100]; $p = 0.040$; NNT [95% CI]: 18 [9, 334]; Fig. 1). When the remission cut-off was increased to a MADRS total score of 12, 38.7% (130/336) of esketamine nasal spray-treated patients achieved remission at Week 8 compared with 22.9% (78/340) of quetiapine extended release-treated patients (relative risk: 1.695 [1.338, 2.149]; $p < 0.001$; NNT: 7 [5, 12]; Fig. 1).

A significantly greater proportion of esketamine nasal spray-treated patients remained relapse-free through Week 32 after achieving remission at Week 8 (21.7%; 73/336) compared with quetiapine extended release-treated patients (14.1%; 48/340; relative risk: 1.552 [1.115, 2.160]; $p = 0.009$; NNT: 13 [8, 50]).[17] All sensitivity analyses for the key secondary end-point favoured esketamine nasal spray over quetiapine extended release, with relative risks ranging from 1.417 to 1.838 (all $p < 0.05$; Fig. 2). Where the remission cut-off was changed to a MADRS total score of 8, 15.2% (51/336) of esketamine nasal spray-treated patients remained relapse-free through to Week 32 after achieving remission at Week 8 compared with 9.7% (33/340) of quetiapine extended release-treated patients (relative risk: 1.573 [1.041, 2.378]; $p = 0.032$; NNT: 19 [10, 167]; Fig. 2). Where the remission cut-off was increased to a MADRS total score of 12, 32.1% (108/336) of esketamine nasal spray-treated patients remained relapse-free at Week 32 after achieving remission at Week 8 compared with 17.6% (60/340) of quetiapine extended release-treated patients (relative risk: 1.838 [1.396, 2.419]; $p < 0.001$; NNT: 7 [5, 13]; Fig. 2).



	Main analysis (remission cut-off of MADRS ≤10)	Remission cut-off of MADRS ≤8	Remission cut-off of MADRS ≤12	Remission at Week 6	Remission at Week 10	Remission within 8 weeks
Relative risk (95% CI)	1.542 (1.153–2.063) $p = 0.003$	1.462 (1.017–2.100) $p = 0.040$	1.695 (1.338–2.149) $p < 0.001$	1.510 (1.083–2.105) $p = 0.015$	1.568 (1.202–2.046) $p = 0.001$	1.737 (1.343–2.248) $p < 0.001$
Odds ratio (95% CI)	1.740 (1.204–2.515) $p = 0.003$	1.557 (1.023–2.370) $p = 0.038$	2.142 (1.530–2.998) $p < 0.001$	1.642 (1.104–2.441) $p = 0.014$	1.824 (1.283–2.594) $p = 0.001$	2.125 (1.504–3.004) $p < 0.001$
Risk difference (95% CI)	9.5 (3.3–15.8) $p = 0.003$	5.8 (0.3–11.3) $p = 0.038$	15.9 (9.0–22.7) $p < 0.001$	7.3 (1.5–13.1) $p = 0.013$	11.3 (4.8–17.8) $p = 0.001$	14.9 (8.2–21.6) $p < 0.001$
NNT (95% CI)	11 (7–31)	18 (9–334)	7 (5–12)	14 (8–67)	9 (6–21)	7 (5–13)

Fig. 1 Proportion of patients achieving remission at Week 8 (primary end-point) per sensitivity analysis. The primary end-point was achieving remission (MADRS total score ≤10) at Week 8. CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; NNT, number needed to treat; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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Remission over time using cut-offs of MADRS scores of 8, 10 and 12

A greater proportion of esketamine nasal spray-treated patients achieved MADRS scores of ≤10 remission at each timepoint from Week 2 to Week 32 compared with quetiapine extended release-treated patients. Relative risks ranged from 1.366 to 2.745 (Fig. 3). At Week 8, 27.1% (91/336) of esketamine nasal spray-treated patients achieved remission versus 17.6% (60/340) of quetiapine extended release-treated patients (relative risk: 1.542 [1.153, 2.063]; $p = 0.003$). At Week 32, 49.7% (167/336) of esketamine nasal spray-treated patients achieved remission versus 32.9% (112/340) of quetiapine extended release-treated patients (relative risk: 1.515 [1.259, 1.823]; $p < 0.001$).

Results were similar for the achievement of MADRS score of ≤8 remission (Week 8: 18.5% [62/336] esketamine nasal spray-treated patients, 12.6% [43/340] quetiapine extended release-treated patients, relative risk: 1.462 [1.017, 2.100], $p = 0.040$; Week 32: 37.5% [126/336] esketamine nasal spray-treated patients, 23.2% [79/340] quetiapine extended release-treated patients, relative risk: 1.621 [1.279, 2.054], $p < 0.001$). Results were also similar for the achievement of MADRS score of ≤12 remission (Week 8: 38.7% [130/336] esketamine nasal spray-treated patients, 22.9% [78/340] quetiapine extended release-treated patients, relative risk: 1.695 [1.338, 2.149], $p < 0.001$; Week 32: 57.7% [194/336] esketamine nasal spray-treated patients, 40.9% [139/340] quetiapine extended release-treated patients, relative risk: 1.418 [1.213, 1.658], $p < 0.001$).

Results using the LOCF approach were similar and demonstrated the superiority of esketamine nasal spray (Supplementary Figure 2).

Time to first and confirmed remission and response

Treatment with esketamine nasal spray shortened the time to first remission versus quetiapine extended release (hazard ratio: 1.711 [1.402, 2.087]; $p < 0.001$; Figs. 4(a) and 4(b)). The same result was seen in time to confirmed remission (hazard ratio: 1.658 [1.337, 2.055]; $p < 0.001$).

Treatment with esketamine nasal spray also shortened the time to first response (hazard ratio: 1.848 [1.547, 2.207]; $p < 0.001$) and confirmed response (hazard ratio: 1.809 [1.505, 2.174]; $p < 0.001$) versus quetiapine extended release (Figs. 4(c) and 4(d)).

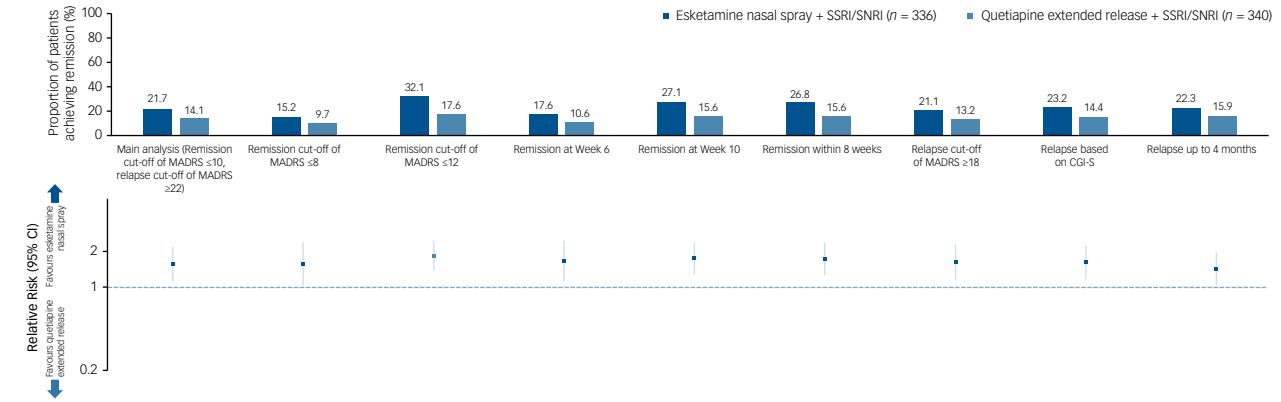
Hazard ratios displayed in a forest plot can be found in Supplementary Figure 3.

There was minimal impact of remote versus in-person MADRS assessments on the estimated difference between esketamine nasal spray and quetiapine extended release on MADRS change from baseline at each visit (Supplementary Appendix 2, Supplementary Table 3).

Discussion

Remission and prevention of relapse are well recognised as main treatment goals of treating depression. However, there is a lack of a consensus in the TRD field regarding how to best define remission and relapse. Varied definitions using different timelines, scales and thresholds are used in the literature,[5,18–20] the most notable of which were used to define the sensitivity analyses reported here. Depending on the sensitivity analysis, esketamine nasal spray-treated patients were 46.2–73.7% relatively more likely to achieve remission at Week 8 (primary end-point), and 41.7–83.8% relatively more likely to be relapse-free after remission at Week 8 (key secondary end-point) than quetiapine extended release-treated patients. Additional analyses of remission over time and time to remission and response all significantly favoured esketamine nasal spray over quetiapine extended release. Even using the most conservative of the pre-specified cut-offs (MADRS score of ≤8), esketamine nasal spray still showed superiority over quetiapine extended release at Week 6 through Week 32. Confidence intervals were largely overlapping between all sensitivity analyses and with the main analysis; even if there were a difference in point estimates, the results remained highly consistent. These extensive sensitivity analyses show the conclusions of the study remain unchanged, thereby reinforcing the strength of the initial findings.[17]

MADRS cut-off scores of 8, 10 and 12 each demonstrate that remission rates continued to increase beyond Week 8 in both treatment arms. Esketamine nasal spray maintained superiority over



Relative risk (95% CI)	1.552 (1.115–2.160) $p = 0.009$	1.573 (1.041–2.378) $p = 0.032$	1.838 (1.396–2.419) $p < 0.001$	1.666 (1.130–2.455) $p = 0.010$	1.749 (1.292–2.368) $p < 0.001$	1.730 (1.277–2.345) $p < 0.001$	1.612 (1.147–2.265) $p = 0.006$	1.621 (1.171–2.242 $p = 0.004$	1.417 (1.034–1.942) $p = 0.030$
Odds ratio (95% CI)	1.717 (1.146–2.571) $p = 0.008$	1.674 (1.050–2.671) $p = 0.029$	2.278 (1.580–3.285 $p < 0.001$	1.806 (1.157–2.822) $p = 0.009$	2.039 (1.392–2.986) $p < 0.001$	2.007 (1.370–2.941) $p < 0.001$	1.791 (1.185–2.707) $p = 0.005$	1.811 (1.219–2.692) $p = 0.003$	1.543 (1.044–2.281) $p = 0.029$
Odds ratio (95% CI)	7.7 (2.0–13.5) $p = 0.008$	5.5 (0.6–10.5) $p = 0.029$	14.7 (8.3–21.0) $p < 0.001$	7.0 (1.8–12.2) $p = 0.008$	11.6 (5.5–17.7) $p < 0.001$	11.3 (5.2–17.4) $p < 0.001$	8.0 (2.4–13.6) $p = 0.005$	8.9 (3.0–14.7) $p = 0.003$	6.6 (0.7–12.5) $p = 0.028$
NNT (95% CI)	13 (8–50)	19 (10–167)	7 (5–13)	15 (9–56)	9 (6–19)	9 (6–20)	13 (8–42)	12 (7–34)	16 (8–143)

Fig. 2 Proportion of patients remaining relapse-free through Week 32 after achieving remission at Week 8 (key secondary end-point) per sensitivity analysis. The key secondary end-point was remaining relapse-free though to Week 32 after achieving remission at Week 8. CGI-S, Clinical Global Impression-Severity scale; CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; NNT, number needed to treat; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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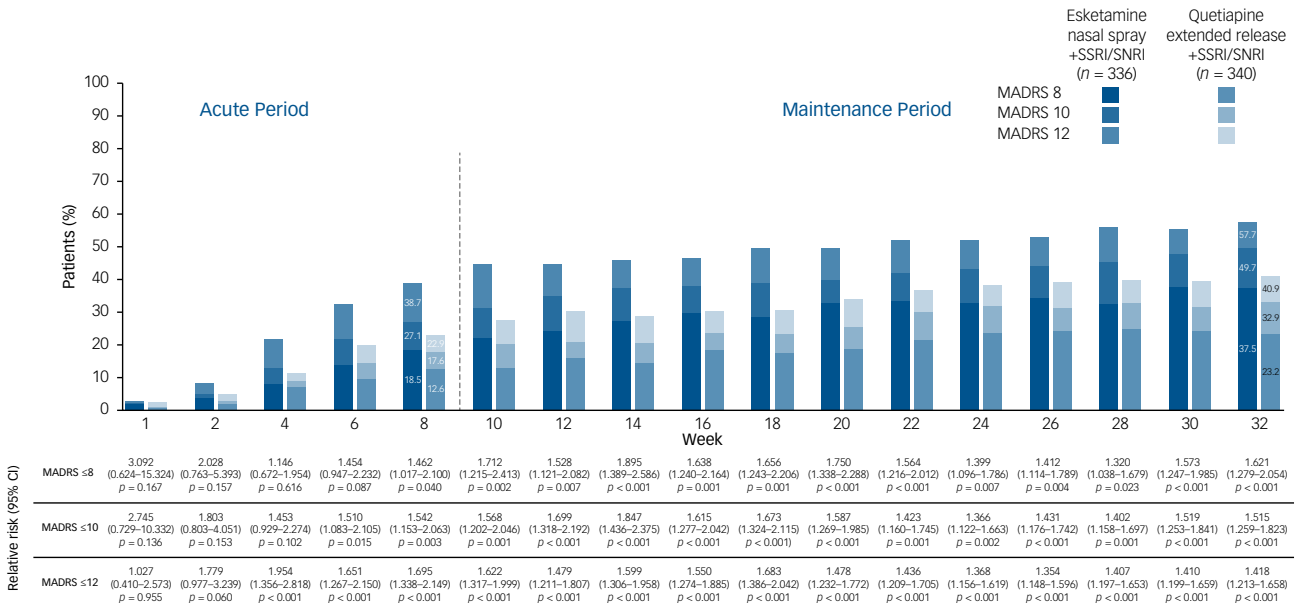

Fig. 3 Remission over time using MADRS 8, 10 and 12 cut-offs (non-responder imputation). Full analysis set. CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

quetiapine extended release at each timepoint. By Week 32, there was a larger proportion of esketamine nasal spray patients, compared with quetiapine extended release, that achieved remission regardless of the MADRS cut-off score used. These data demonstrate that remission can be achieved after Week 8, and remission at a later timepoint is still beneficial to the patient.

Whilst these analyses provide the overall remission rates at population level, it is not necessarily the same patients in remission from one visit to the next. To focus more on individual patient trajectories, time to remission and response analyses were conducted. These results also illustrate that esketamine nasal spray shortens time to remission and response compared with quetiapine extended

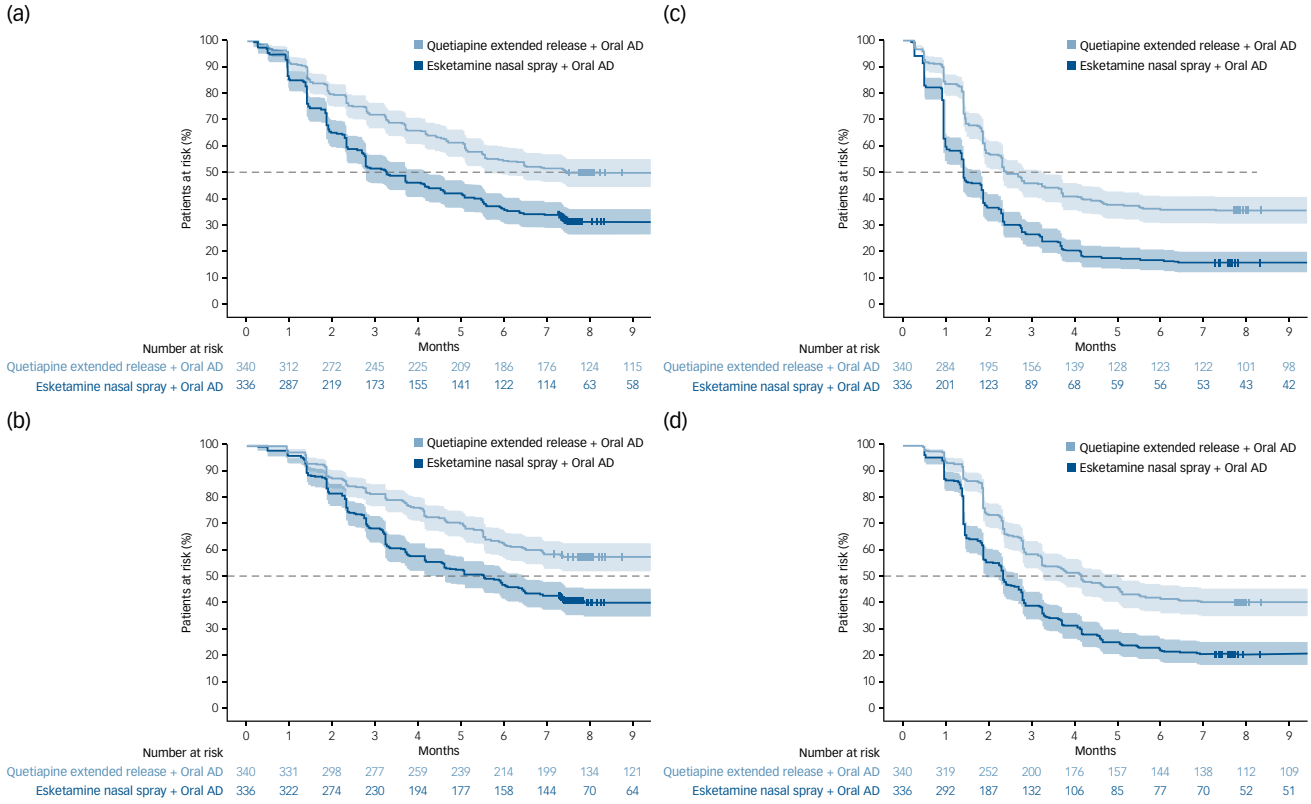

Fig. 4 Time to Montgomery–Åsberg Depression Rating Scale (a) and (b) first and confirmed remission and (c) and (d) first and confirmed response. Full analysis set. Month 2 corresponds to Week 8, and Month 8 corresponds to Week 32. AD, antidepressant.

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release. Patients with TRD, for the most part, have endured long depressive episodes without relief, so enabling them to reach remission in a shorter amount of time is pertinent. In addition, these time to event analyses provide a time-based component to this analysis where before only binary end-points were reported for the ESCAPE-TRD study.[17] Esketamine nasal spray not only increases the proportion of patients achieving remission at a specific time, but also decreases the time it takes to reach remission. Hazard ratios for time to remission and response both favoured esketamine nasal spray over quetiapine extended release.

Strengths and limitations

To our knowledge, ESCAPE-TRD is the first randomised comparative study reporting long-term esketamine nasal spray use against an augmentation treatment for patients with TRD. To provide further evidence using various definitions of remission and relapse from the literature, these additional analyses of the primary and key secondary end-points support the overall superiority of esketamine nasal spray over quetiapine extended release.

This study population reflects a patient population that may not be generalisable to the hospital-based population of patients with TRD, where more treatment trials may have occurred before initiation of esketamine nasal spray treatment. There are potential non-specific effects that were not equal between treatment groups. Given the single-blind (raters unaware of treatment assignment), open-label design of this study, this may have introduced some chance of premature discontinuation owing to patient knowledge of their study treatment. In addition, patients in the esketamine nasal spray arm had a higher number of clinic visits in the acute phase owing to the administration method, as esketamine nasal spray required physician oversight whilst quetiapine extended release was self-administered. Furthermore, quetiapine extended release was titrated rapidly to the final dose, which may have decreased tolerability. These elements of the study design were difficult to account for and may have influenced perceptions of efficacy; however, the treatment visit schedule did accurately reflect clinical practice for esketamine nasal spray treatment.

Future directions

While additional study is required, these sensitivity analyses potentially further support the patient benefit of continuing use of esketamine nasal spray even if remission is not achieved by Week 8. Some current regulations recommend that esketamine nasal spray be discontinued if remission is not achieved before or by Week 8.[23] Additional data should be collected to determine if longer treatment with esketamine nasal spray may be beneficial, or when esketamine nasal spray treatment should be stopped if remission is not achieved. These data could also explore how esketamine nasal spray should be tapered off, and if weekly or biweekly treatment is favourable.

Further work could include analyses of patient-reported outcomes. Whilst improvements in TRD can be measured with clinical scores, it is important to consider improvements in measures that incorporate the patient experience and patient voice. In addition, further analyses could examine esketamine nasal spray versus quetiapine extended release in subgroups of patients, such as age, number of prior treatment failures or patients with generalised anxiety disorder, to determine the effect of esketamine nasal spray treatment in these groups.

All sensitivity analyses favoured esketamine nasal spray over quetiapine extended release, which confirmed the robustness of the primary and key secondary results of the ESCAPE-TRD study.[17] Additional analyses on remission beyond Week 8 provided additional perspective on the long-term benefit of esketamine nasal spray compared with quetiapine extended release. Furthermore, time to remission and response analyses demonstrated that esketamine nasal spray shortened time to remission and time to response.

These findings all further support the superiority of esketamine nasal spray compared with quetiapine extended release in achieving treatment goals in both the acute and the maintenance phase in patients with TRD and provide guidance to clinicians about the use of esketamine nasal spray.

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Supplementary material

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Data availability

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) project site at http://yoda.yale.edu.

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Author contributions

Substantial contributions to study conception and design: A.H.Y., P.M.L., A.F., P.F., N.C., R.E.N., O.B., Y.G., B.R., J.D., S.M.H., A.R.; substantial contributions to analysis and interpretation of the data: A.H.Y., P.M.L., A.F., P.F., N.C., R.E.N., O.B., Y.G., B.R., J.D., S.M.H., A.R.; drafting the article or revising it critically for important intellectual content: A.H.Y., P.M.L., A.F., P.F., N.C., R.E.N., O.B., Y.G., B.R., J.D., S.M.H., A.R.; final approval of the version of the article to be published: A.H.Y., P.M.L., A.F., P.F., N.C., R.E.N., O.B., Y.G., B.R., J.D., S.M.H., A.R.

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Transparency declaration

The lead author and manuscript guarantor affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. A.H.Y. is a member of the British Journal of Psychiatry editorial board, and can confirm that he did not take part in the review or decision-making process of this manuscript.

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Janssen EMEA were responsible for study design and analysis of the data. Authors, including those affiliated with Janssen EMEA, were involved in drafting the outline of this manuscript and in reviewing subsequent drafts. Janssen EMEA did not provide any suggestions to authors. Final approval of the manuscript was the sole decision of the authors.

Declaration of interest

A.H.Y.: In the past 3 years received consulting fees and speaker's honoraria from Allegan, AstraZeneca, Bionomics, Eli Lilly, Janssen, Johnson & Johnson, LivaNova, Lundbeck, Servier, Takeda and Sumitomo Dainippon Pharma and Sunovion; received grants from Janssen; independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley National Health Service (NHS) Foundation Trust and King's College London; the views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Professor A.H. Young is a member of the British Journal of Psychiatry editorial board, and can confirm that he did not take part in the review or decision-making process of this manuscript. P.M.L.: In the past 3 years participated in advisory boards for Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche and Rovi; received speaker's honoraria and consultation fees from Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche and Rovi; member of the executive committee of Fondation FondaMental. Involved in developing national care guidelines for the French Society for Biological Psychiatry and Neuropsychopharmacology on the treatment of major depression. A.F.: Consulted for, received grants from or participated as a speaker in symposia sponsored by Angelini, Apsen, Biogen, Boehringer Ingelheim, Janssen, Lundbeck, Mylan, Novartis, Otsuka, Pfizer, Recordati, Rovi and Viatris. P.F.: Served on advisory boards for and received speaker's honoraria from Boehringer Ingelheim, Janssen and Richter. N.C.: Served on advisory boards and received speaker's honoraria from Angelini, Esteve, Janssen, Lundbeck, Novartis, Pfizer and Viatris. Furthermore, they have been awarded research grants from the Ministry of Health, Ministry of Science and Innovation (CIBERSAM) and the Strategic Plan for Research and Innovation in Health (PERIS) for the period 2016–2020, as well as from Marato TV3 and Recercaixa. R.E.N.: Received funding from or acted as a principal investigator for Boehringer Ingelheim, Compass, Janssen-Cilag, Lundbeck and Otsuka Pharmaceuticals; received speaker's fees from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka Pharmaceuticals, Servier and Teva; has been an advisor to AstraZeneca, Eli Lilly, Janssen-Cilag, Lundbeck, Medivir, Otsuka Pharmaceuticals and Takeda. O.B.: Received speaker's honoraria from Janssen and Lundbeck, served on advisory board for Janssen, participated as principal investigator on the ESCAPE-TRD study, Janssen. Y.G., B.R.: Employees of Janssen. J.D., S.M.H.: Employees of Janssen; hold Johnson & Johnson company stocks/stock options. A.R.: In the past 3 years received speaker's honoraria from Janssen, Medice, Shire/Takeda and Das Fortbildungskolleg; participated in advisory boards for Boehringer Ingelheim, Compass, Cyclerion, Janssen, LivaNova, Medice, SAGE/Biogen and Shire/Takeda; participated without financial compensation in a data and safety monitoring board for the GAINS study; participated without financial compensation in the Scientific and Ethics Advisory Board for the European Union (EU) H2020 project, TIMESPAN; received support for attending meetings from Janssen; board member of Deutsche Gesellschaft für Bipolare Störungen (DGBS), Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), European College of Neuropsychopharmacology (ECNP) and the German Depression Foundation; aided in developing national care guidelines (NVL, S3) on major depression, bipolar disorder, attention-deficit hyperactivity disorder (ADHD), and suicidal behaviour.

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