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 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.
- Treatment-resistant depression (TRD) is commonly defined as non-response to ≥2 consecutive treatments at adequate dosage and duration in the current depressive episode.1
- In the ESCAPE-TRD (NCT03060821), 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 8.2

OBJECTIVE

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

METHODS

- Patients were randomised 1:1 to esketamine NS or quetiapine XR, alongside an imitated-placebo group, to treat depressive episodes using 1 of any non-antidepressant medications inhibited by or not inhibited by the phosphodiesterase-4 (PDE-4) inhibitor GSK573265.3
- Randomisation was stratified by age (18–65 years) and prior treatment failure (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 patients with 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 as an infinite (potentially large) time and were assumed to never achieve remission.

RESULTS

- Baseline characteristics, including consecutive prior treatment failures, were consistent between randomisation groups and have been reported previously.4
- A significantly greater proportion of patients with ≥2 prior treatment failures achieved remission at week 8 with esketamine NS versus quetiapine XR: 26.5% (95% CI: 15.8–37.2) versus 7.8% (95% CI: 4.4–13.1), p<0.001 (Figure 3A).
- A significantly greater proportion of patients with ≥3 prior treatment failures achieved remission at week 8 with esketamine NS versus quetiapine XR: 18.2% (95% CI: 7.8–26.5) versus 7.8% (95% CI: 4.4–13.1), p<0.001 (Figure 4A).
- Significantly greater proportions of patients with ≥2 or ≥3 prior treatment failures were relapse-free through week 32 after remission at week 8 with esketamine NS versus quetiapine XR: 23.8% (95% CI: 12.1–35.7) versus 11.6% (95% CI: 6.5–19.9), p<0.05 (Figure 3B).
- Esketamine NS significantly improved time to relapse versus quetiapine XR in both subgroups (≥2 prior treatment failures: HR: 2.583 [1.468, 4.545], p=0.013; ≥3 prior treatment failures: HR: 2.066 [1.469, 2.887], p<0.001) (Figure 4B).
- A greater percentage of patients who achieved remission increased over time for patients with ≥2 failures (Figure 4A) and ≥3 failures (Figure 4B) in both treatment arms, and was consistently higher for the esketamine NS arm compared with quetiapine XR.

SUMMARY

Esketamine NS significantly increased time to relapse in patients with ≥2 and ≥3 prior treatment failures, with patients ≥2 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 anytime, 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.