Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined with a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1)

BACKGROUND

- About one-third of patients with MDD fail to achieve remission despite treatment with multiple biogenic amine (e.g., serotonin, norepinephrine) antidepressants and hence have treatment-resistant depression (TRD).
- There is an unmet need to develop novel treatments providing effective, more rapid-acting, and sustained or long-term relief of depressive symptoms, especially in patients with TRD.
- A nasal spray formulation of esketamine was recently been approved for TRD treatment.

OBJECTIVE

- Compare the efficacy and safety of fixed doses of esketamine nasal spray plus a newly initiated oral antidepressant to a newly initiated oral antidepressant (active comparator) plus a placebo nasal spray in adult patients with TRD.

METHODS

- **Design**: Multisite, double-blind, randomized parallel trial; Duration: 4 weeks
- **Inclusion criteria**: Nonresponse to an adequate therapeutic trial (established by considering dose, duration, and adherence) of at least 2 different antidepressants within the current episode of depression; recurrent MDD or single-episode MDD (≥2 years) without psychotic features; moderate-to-severe depression.
- **Exclusion criteria**: Suicidal ideation with intent to act within the prior 6 months or suicidal behavior within the prior year; diagnosis of psychotic disorder, bipolar or related disorders; recent history (within prior 6 months) of moderate or severe substance use disorder; positive test result(s) for specified drugs of abuse.
- **Primary outcome measure**: Change from baseline to day 28 in the Montgomery-Asberg Depression Rating Scale total score.
- **Secondary outcome measures**: Onset of clinical response by day 2 (24 hours) that was maintained; change from baseline in SDS and PHQ-9 total score at day 28.
- 346 patients were randomly assigned 1:1:1 to treatment with:
    - BIW esketamine 56 mg + a newly initiated, open-label, oral antidepressant taken daily (n=117)
    - BIW esketamine 84 mg + a newly initiated, open-label, oral antidepressant taken daily (n=116) OR
    - BIW placebo + a newly initiated, open-label, oral antidepressant taken daily (n=113)
- A maximum sample size of 348 individuals to achieve 90% power was planned assuming a treatment difference of 6.5 points in MADRS total score between either dose of esketamine/antidepressant and antidepressant/placebo, a SD of 12, a 2-sided significance level of .025, and a drop-out rate of 25%.
- Data were analyzed based on analysis sets that included all randomized patients who received at least 1 dose of intranasal study medication and 1 dose of oral anti-depressant.

RESULTS

- 315 patients completed the study: 111 in esketamine 56 mg group, 97 in esketamine 84 mg group, 107 in placebo group.
- **Primary outcome measure**: The difference between the esketamine 84 mg/antidepressant and the antidepressant/placebo groups for the change in MADRS total score was not statistically significant (P = .088).
- **Secondary outcome measures**: Could not be formally evaluated based on the predefined testing sequence. Results of all key secondary efficacy endpoints numerically favored both esketamine/antidepressant treatment groups over antidepressant/placebo.
- **Author's conclusion**: Although esketamine 84 mg/antidepressant was not statistically significant relative to antidepressant/placebo, the treatment differences at day 28 of –3.2 and –4.1 for the esketamine 84 mg/ antidepressant and esketamine 56 mg/antidepressant groups, respectively, appear consistent with the positive findings in a similar, Phase 3 flexible-dose esketamine study in adults with TRD.

STRENGTHS

- Random assignment stratified by country and class of oral antidepressant
- Use of identical placebo
- Use of remote raters to assess outcomes

LIMITATIONS

- Short study duration
- High dropout rate
- Higher placebo effect than expected
- Likely unblinding
- Imbalances in baseline demographics among treatment groups

CONCLUSION

- The statistical significance was not achieved for esketamine 84 mg/antidepressant compared with antidepressant/placebo; However, data for esketamine 56 mg/antidepressant suggest some clinical benefits.
- Although this drug has shown some early benefits, the clinical usefulness is still to be established.
- Future studies with a longer duration and larger samples are needed to assess efficacy and serious adverse effects.

Reference: Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). Int J Neuropsychopharmacol. 2019;22(10):616-630.

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