Effect of Esketamine Nasal Spray on Cognition in Patients With Treatment-Resistant Depression: Results From Five Phase 3 Studies

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INTRODUCTION

- Major depressive disorder (MDD) is a debilitating psychiatric illness and is a major contributor to the overall global burden of disease.1
- Nearly one-third of patients with MDD do not respond to available antidepressants (AD) and develop treatment-resistant depression (TRD).1,2
- The growing prevalence of TRD and the poor response rates to ADs, highlight the need for novel treatments that can provide rapid and sustained relief of depressive symptoms in patients with TRD.

Esketamine (Esk), the N-methyl-D-aspartate (NMDA) receptor antagonist being developed as an intranasal formulation for therapy in TRD.

- We evaluate the cognitive effects of Esk nasal spray in patients with TRD in five phase 3, multicenter studies: 3 acute randomized, double-blind (DB) studies (DB1, DB2, DB4), 1 maintenance of effect study (randomized withdrawal design, DB3) and 1 open-label (OL) study (OL1).

METHODS

- Study designs were used to summarize group mean scores and changes from baseline scores for the primary performance measure from each cognitive test and scores were plotted at each scheduled timepoint.

RESULTS

Study Population

<table>
<thead>
<tr>
<th>Test</th>
<th>DB1</th>
<th>DB2</th>
<th>DB4</th>
<th>Total</th>
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<tbody>
<tr>
<td>0</td>
<td>152</td>
<td>156</td>
<td>156</td>
<td>464</td>
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<tr>
<td>3 weeks</td>
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<td>52 weeks</td>
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<td>102</td>
<td>102</td>
<td>306</td>
</tr>
<tr>
<td>104 weeks</td>
<td>102</td>
<td>102</td>
<td>102</td>
<td>306</td>
</tr>
</tbody>
</table>

- All cognitive tests were conducted predrug at baseline, day 28, early withdrawal (EW), and follow-up phase (F/U, week 2) in DB1, DB2, DB4, and at 12 weeks interim, beginning from week 36 (DB1, 20 [OL1], EW and F/U) (DB2, 3 weeks; DB1, 4 weeks).
- Cognitive assessments were also administered at baseline and day 28 for direct entry patients in DB3 or patients in OL1 (including elderly non-responders from DB3) and at EW visits.

Statistical Analyses

- Direct comparisons were used to summarize group mean scores and changes from baseline scores for the primary performance measure from each cognitive test and scores were plotted at each scheduled timepoint.

RESULTS

- Among patients ≥ 65 years in OL1, mean performance on simple and choice RT tests (DET and DNI) slowed from baseline, beginning at week 20 (n = 72) and continuing through week 52 endpoint (n = 24).
- For patients ≥ 65 years who completed through week 52 (n = 24 with baseline and week 52 assessment results) mean (SD) slowing for week 52 (DET = 0.0184, SD = 0.1037; DNI = 0.0099; SD = 0.05574; Cohen’s d = 0.05 endpoint (week 52) change from baseline slowdown of 0.01 and 0.0; for choice RT d = 0.47.

DISCUSSION/CONCLUSION

- Cognition generally remained stable in adult and elderly patients with TRD during acute and long-term treatment with either Esk or oral AD or oral AD plus placebo.
- Patients ≥ 65 years in OL1 exhibited RT slowing during EW/MA, but this was inconsistent with large increases and large decreases over time within individuals. No elderly participants exhibited impaired RT at both endpoint and F/U; some met criteria for slowing at F/U but not at week 52 endpoint. Performance of patients aged ≥ 65 remained stable on all other cognitive tests during all OL1.
- Based on data from the Australian Imaging, Biomarkers and Lifestyle (AIBL) trial, Maruff2014, personal communication estimated 1-year age-related slowing on a RT test consistent with a > 1 standard deviation (SD) slowing compared to healthy elderly, 0.47 (average of DET and DNI z-scores using AIBL baseline mean and SD). On the same composite, we did see slowing among OL1 patients > 52 weeks (completers) ≥ 0.56 on the same composite (but basing the z-scores on Cogstate age-adjusted norms).
- Generalization of week 52 findings for patients ≥ 65 years in OL1 is limited by small sample size, and the absence of an elderly control group with TRD who received AD plus PRO across the same time frame.
- Due to absence of a comparator arm, the cause(s) of RT slowing cannot be concluded.
- There appeared to be no meaningful associations between clinical or treatment parameters and RT performance, including esketamine dose.
- There are no longitudinal studies of RT in elderly TRD patients for comparison, and we expected magnitude of RT slowing, or whether this population could be more susceptible to amotivation or testing fatigue on timed tests, is unknown.

REFERENCES


This study was supported by funding from Janssen Research & Development LLC, Titusville, NJ, USA.

Presented at The American College of Neuropsychopharmacology (ACNP) 57th Annual Meeting, December 9-13, 2018, Hollywood, FL, USA.