Poster No. 89

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).[2,3]
- The growing prevalence of TRD and the poor response rates to ADs[4] , highlight the need for novel treatments that can provide rapid and sustained relief of depressive symptoms in patients with TRD.
- Esketamine (ESK), the S-enantiomer of ketamine, is a N-methyl-D-aspartate (NMDA) receptor antagonist being developed as an intranasal formulation for therapy in TRD[5].
- 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 (randomised withdrawal design, DB3) and 1 open-label (OL) study (OL1).

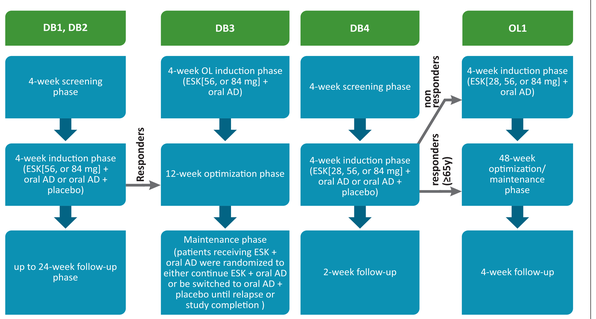
METHODS

Key inclusion criteria (all studies): Adult patients (18-64 years [≥65 years for DB4; >18 for OL1]) with moderate-to-severe depression and non-response to ≥2 AD in the current depressive episode were enrolled.

Study Design

- **DB studies 1, 2 and 4:** Patients were randomized either to placebo + newly-initiated oral AD (oral AD), or fixed dose ESK (DB1: 56 or 84 mg) or flexible dose (DB2, DB4: 28 [DB4 only], 56 or 84 mg).
- **Maintenance of effect study (DB3):** Direct entry patients received a 4-week OL IND (ESK 56 or 84 mg)+oral AD, a 12-week optimization phase (OP), and a maintenance phase (MA, randomized withdrawal).
- **OL study (OL1):** Evaluated ESK (28 [≥65 years], 56 or 84 mg) and oral AD.

Study Design



At the end of the 4-week induction phase (IND), responders in DB1 and DB2 were eligible to enter DB3; patients ≥ 65 years in DB4 (regardless of response) were eligible to enter OL1. DB3 included a 4-week OL IND (ESK 56 or 84 mg) + newly-initiated oral AD, a 12-week optimization phase (OP) to individualize treatment session frequency (once-weekly or once every other week), and a maintenance phase (MA) in which patients receiving ESK + oral AD were randomized to either continue ESK + oral AD or be switched to oral AD + placebo until relapse or study completion.
OL1 included a 4-week OL IND (28, 56, or 84 mg) + newly-initiated oral AD, followed by up to a 48-week OP/MA. The follow-up phase (F/U) was 24-weeks (DB1, DB2; for non-responders or those who elected not to go to the DB3), 2-weeks (DB3, DB4), and 4-weeks (OL1).

Cognitive assessments

Table 1. Cognitive assessments

Test type	Test	Cognitive domain assessed
Cogstate® computerized test battery	Detection (DET)	Simple reaction time
	Identification (IDN)	Choice reaction time
	One-Card Learning (OCL)	Visual memory
	One Back Memory (ONB)	Working memory
	Groton Maze Learning (GML)	Executive function
Hopkins Verbal Learning Test-Revised (HVLT-R)	Total Recall	Verbal Learning
	Delayed Recall	Delayed Verbal Memory

- All cognitive tests were conducted predose at baseline, day 28, early withdrawal (EW), and follow-up phase (F/U, week 2) in DB1, DB2, DB4, and at 12 week intervals, beginning from week 16 (DB3) and 20 (OL1), EW and F/U (DB3, 2 weeks; OL1 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 DB4) and at EW visits.

Statistical Analyses

Descriptive statistics were used to summarize group mean scores, and change from baseline scores for the primary performance measure from each cognitive test and scores were plotted at each scheduled timepoint.

RESULTS

Study Population

Table 2. Summary of population analyzed for cognitive assessments

Study	ESK + Oral AD	Oral AD + Placebo	Total
DB1	230	113	343
DB2	115	109	224
DB3 (maintenance phase only)	152	145	297
DB4	72	65	137
OL1			796

- ***Acute studies DB1, DB2 and DB4***: Mean performance in ESK+oral AD and oral AD+placebo groups on each cognitive test generally either improved from, or remained similar to, baseline at both the end of DB treatment (day 28) and during the F/U.
- ***Long-term studies (DB3, OL1)***: Performance on each cognitive test generally either improved from, or remained similar to baseline during optimization (OP) phase, maintenance (MA) phase, OP/MA phase, including those treated with either ESK+oral AD or oral AD + placebo in DB MA phase of DB3 (n = 133 to 145 per group at LOCF endpoint).
- Most observed improvements in performance were small, although, improvements on HVLT-R at weeks 32 and 44 for patients treated with ESK+oral AD or oral AD + placebo in DB3, and for patients treated with ESK+oral AD through week 44 in OL1 were moderate (figure 1 and 2); Cohen's d for effect size at week 44 ranged from 0.2 to 0.68.

Figure 1. DB3: Arithmetic Mean (±SE) of HVLT-R Total Recall

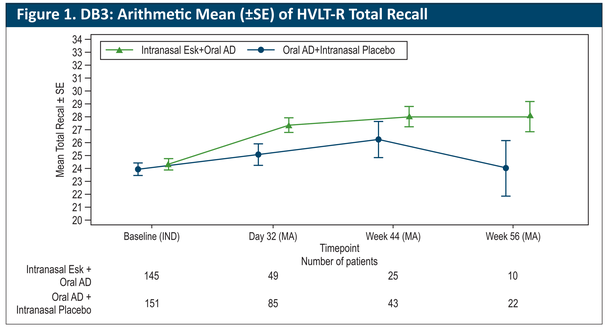
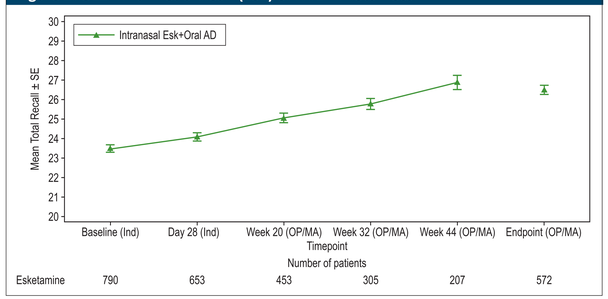
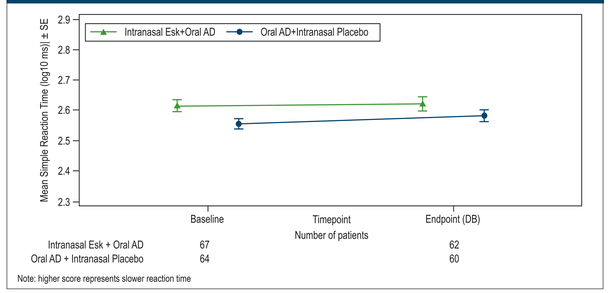


Figure 2. OL1: Arithmetic Mean (±SE) of HVLT-R Total recall



- A slight slowing of reaction time (RT) was observed in patients ≥ 65 years (DB4) at Day 28; mean slowing [log10 ms] from baseline in the ESK + oral AD group = 0.0182; SD = 0.14018 [effect size, change from baseline, Cohen's d = 0.12, n = 56] and in the oral AD+placebo group = 0.0245; SD = 0.13437 [Cohen's d = 0.18, n = 58].

Figure 3. DB4: Arithmetic Mean (±SE) of Detection (Age Group: ≥ 65 years)



- Among patients ≥ 65 years in OL1, mean performance on simple and choice RT tests (DET and IDN) slowed from baseline, beginning at week 20 (n = 72) and continuing through week 52 endpoint (n = 24).
- For patients ≥ 65 years who completed through 52 weeks (n=24 with baseline and week 52 assessment results) mean (log10) slowing at week 52 for DET= 0.0824, SD = 0.1377; IDN = 0.0399, SD = 0.05574; Cohen's d for endpoint (week 52) change from baseline for simple RT = 0.52; and for choice RT = 0. 47.

Figure 4. OL1: Arithmetic Mean (±SE) of Detection (Age Group: ≥ 65 years, Completers)

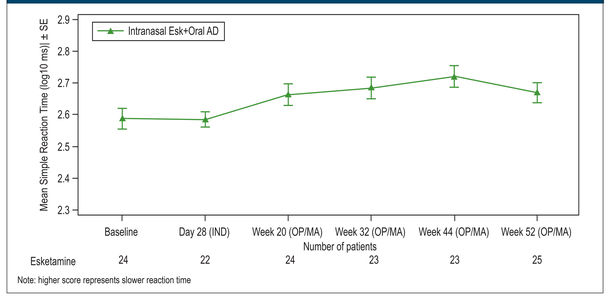
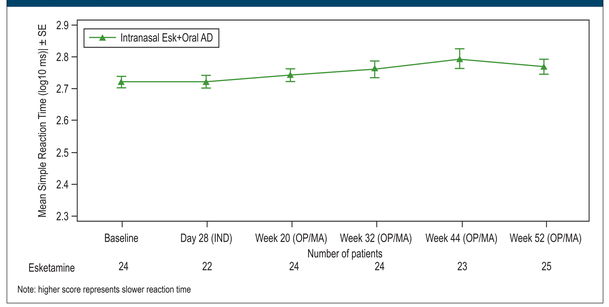
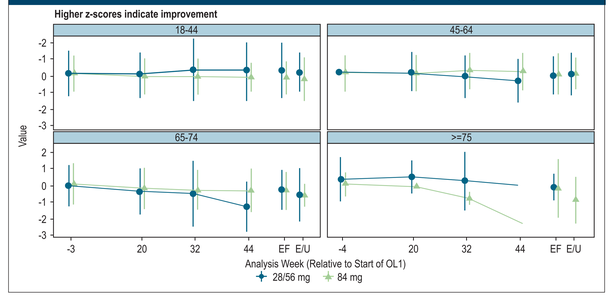


Figure 5. OL1: Arithmetic Mean (±SE) of Identification (Age Group: ≥ 65 years, Completers)



- Patients ≥ 65 years were inconsistent on simple and choice RT during OL1, with large increases and large decreases over time within patients. Reliable Change Index (RCI) and z-score criteria were used to evaluate changes in RT performance of Patients ≥ 65 yearswho completed through week 52 and whose RT was not slowed at baseline (i.e., in patients with baseline z-score > -1.5 on DET and IDN; n=20). Using RCI < -1.645 to define meaningful slowing of RT:
  - Through week 52 endpoint, 7 patients had a meaningful slowing of RT from baseline on 2 or more consecutive post-baseline assessments for either the DET or IDN test, without subsequent recovery of RT performance (defined as RCI vs baseline ≥-1.645)
  - 2 patients had a meaningful slowing of RT versus baseline on 2 or more consecutive post-baseline assessments for both the DET and IDN tests, without subsequent recovery of RT performance
  - No patient who completed cognitive testing at endpoint (week 52) and F/U had impaired RT on simple or choice RT tests (z-score ≤-1.5 on DET or IDN) at both endpoint and F/U. Three patients met criteria for slowed RT at F/U but not endpoint.
- Clinical and treatment-related parameters, including modal dose of esketamine, showed poor correlation with reaction time (Figure 6)

Figure 6. OL1: Detection Test – Mean Change in z-score Over Time by Age Group and Modal Esketamine Dose in OP/MA – Observed Case (All Enrolled Analysis Set)



- Performance of patients ≥ 65 years on all tests of higher cognition (OCL, ONB, GML, HVLT-R) either remained stable or improved throughout OL1.

DISCUSSION/CONCLUSION:

- Cognition generally remained stable in adult and elderly patients with TRD during acute and long-term treatment with either ESK + oral AD, or oral AD + placebo.
- Patients ≥ 65 years in OL1 exhibited RT slowing during OP/MA, but RT 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 throughout OL1.
- Based on data from the Australian Imaging, Biomarkers and Lifestyle (AIBL) trial, Maruff (2018, personal communication) estimated 1-year, age-related slowing on a RT composite score (average of DET + IDN) in healthy elderly = 0.07 (average of DET and IDN z-scores using AIBL baseline mean and SD). On the same composite, week 52 slowing among OL 1 patients ≥ 65 years (completers) = 0.66 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 PBO 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 so expected magnitude of RT slowing, or whether this population may be more susceptible to amotivation or testing fatigue on timed tests, is unknown.

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DISCLOSURES:
Dr. Paul Maruff is an employee of Cogstate Ltd. All other authors are employees of Janssen Research & Development, LLC, and shareholders of Johnson & Johnson. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to present these data.

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