Use of the International Shopping List Test as the objective assessment of cognitive impairment to identify subjects with early Alzheimer’s disease in the Eisai elenbecestat MissionAD Phase 3 clinical trials

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Methods

- Clinical sites identified individuals who they believed would meet the criteria of early AD (MMSE ≥24; Clinical Dementia Rating [CDR]-global score [GS] ≥0.5; CDR Memory Box ≥0.5) for entry into the elenbecestat MissionAD clinical trials
- The ISLT learning and delayed recall trials were administered as the sole objective cognitive assessment for study inclusion
- ISLT scores for eligibility were set at ≥1 SD below age-matched norms, as per NIA-AA 2011 criteria for establishing a research diagnosis of MCI due to AD
- Individuals completed the Cogstate Brief Battery (CBB) between the ISLT learning and delayed recall trials as the required distractor (Figure 2); CBB data enabled comparative analysis with the ISLT

Figure 2. Testing protocol

- The CBB consisted of 4 tasks testing different cognitive aspects including:
  - Detection – psychomotor function and simple reaction time. Measure is speed of response
  - Identification – attention and choice reaction time test. Measure is speed of response
  - One Card Learning – visual learning and memory test. Measure is accuracy of response
  - One Back – working memory test. Measure is speed of response
- Subjects with impaired performance on the ISLT were evaluated for further study inclusion/exclusion criteria including confirmation of amyloid pathology via CSF sampling or PET imaging
- Analyses of ISLT data proceeded in 3 stages:
  1. Acceptability of the ISLT was determined by computing the number of individuals who began, but did not complete, the assessment
  2. The number of individuals with memory impairment (i.e., ISLT total or delayed recall performance ≥1 SD below age-matched controls) was expressed according to age and gender
  3. CBB performance was compared between groups with and without memory impairment sufficient for study entry. Estimates of agreement between classification of impairment on the ISLT and classification of impairment on the CBB were computed with the CBB used as the reference

Results

- As of August 2017, 514 study subjects had initiated the ISLT and were included in this analysis
- Subject demographics were mean age=70.15, SD=8.19, range 50–85, 55.1% female
- One subject (0.2%) did not complete the ISLT, indicating high acceptability of the assessment
- Overall, 324 (63.0%) subjects were classified as having memory impairment on either the ISLT learning score, the ISLT delayed recall score (Figure 3)
- The ISLT immediate recall score and delayed recall scores were significantly correlated (Pearson correlation=0.766, p<0.0001)
- Memory impairment increased with increasing age (Figure 4) and was more common in males (70.6% impaired) compared to females (56.9%)

Statistics

- Cohen’s d was used to express the magnitude of the difference between groups as an effect size. By convention, the magnitude of the Cohen’s d value can be considered small=0.2, medium=0.5 and large=0.8

Conclusions

- The acceptability results demonstrate that the ISLT was appropriate for the age of subjects and stage of dementia
- Both the ISLT immediate and delayed recall tests identified impairment in episodic memory, with a high correlation between the 2 parts of the test
- Performance on the ISLT was also associated strongly with poor performance on independent tests of learning and working memory (CBB)
- Consistency between the ISLT and CBB memory components supports the use of verbal list testing for identifying memory impairment
- In clinical practice, we believe the ISLT or other verbal list learning tests could be used to evaluate memory as long as they are validated for the population being clinically assessed
- This preliminary data supports the continued use of the ISLT as the objective cognitive assessment test for memory impairment in the elenbecestat MissionAD Phase 3 program

References