

# 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

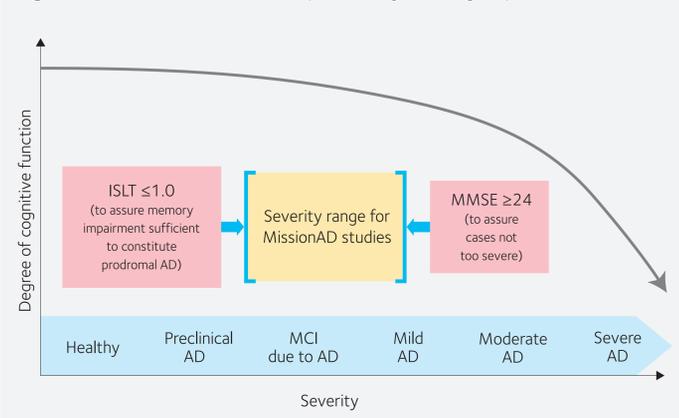
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## Introduction

- Impairment in episodic memory is central to the clinical presentation of dementia due to Alzheimer's disease (AD) as well as the earlier prodromal stage of AD (e.g., mild cognitive impairment due to AD [MCI])
- The National Institute on Aging and the Alzheimer's Association (NIA-AA) recommends the use of objective cognitive testing for the purpose of assessing impairment in individuals in clinical trials for AD and MCI<sup>1</sup>
- Multiple objective measures utilize word lists with immediate and/or delayed recall components which are used in clinical trials for cognitive testing (e.g., Repeatable Battery for Assessment of Neuropsychological Status [RBANS], Mini-Mental State Examination [MMSE], California Verbal Learning Test [CVLT], Rey Auditory Verbal Learning Test [RAVLT], etc.)
- The Eisai elenbecestat\* MissionAD Phase 3 studies are designed to assess the effect of the BACE inhibitor elenbecestat (E2609) on clinical and biomarker outcomes in subjects with early AD
- Given the global footprint of these trials, the objective memory assessment needed to be robust to variations in language, culture, and socio-economic background
- The International Shopping List Test (ISLT) was selected as the objective cognitive measure for the elenbecestat Phase 3 program due to its validity in 90 countries and their corresponding languages
- The ISLT and MMSE are used as inclusion criteria for the Phase 3 studies to ensure selection of individuals with early AD (Figure 1)
- Here, the ability of the ISLT for identifying memory impairment associated with early AD in the ongoing elenbecestat MissionAD Phase 3 program is assessed

Figure 1. ISLT and MMSE help identify the right patients



## International Shopping List Test (ISLT)

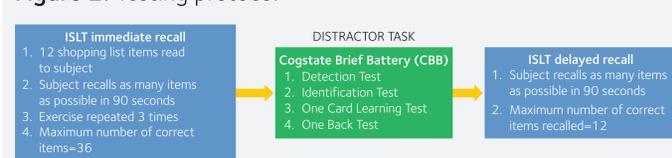
- Verbal list learning test with immediate recall (3 trials) and delayed recall (1 trial) components
- Individuals try to memorize 12 common food items that are read to them
- Test yields 2 performance measures
  - Total recall score for ISLT learning
  - Delayed recall score
- Administered using a computer program, enabling the reading of the shopping list items to the subject by trained staff at a consistent pace
- Scored using Cogstate's automated and secure data processing server against age- and gender-based norms, providing unbiased and immediate results
- Demonstrated sensitivity to the episodic memory impairment seen in dementia and MCI<sup>2,3</sup>
- Validated in 90 languages and their corresponding countries
  - New cultures and language groups are being continually added to the library of available languages, with a formal validation process completed for each new word list<sup>4</sup>

\*proposed International Nonproprietary Name (INN)

## Methods

- Clinical sites identified individuals who they believed would meet the criteria of early AD (MMSE  $\geq 24$ ; Clinical Dementia Rating [CDR]-global score [GS]=0.5; CDR Memory Box  $\geq 0.5$ ) for entry into the elenbecestat 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 memory
  - Detection – psychomotor function and simple reaction time test. 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 other study inclusion/exclusion criteria including confirmation of amyloid pathology via CSF sampling or PET imaging
- Analyses of ISLT data proceeded in 3 stages:
  - Acceptability of the ISLT was determined by computing the number of individuals who began, but did not complete, the assessment
  - The number of individuals with memory impairment (i.e., ISLT total or delayed recall performance  $\geq 1$  SD below age-matched controls) was expressed according to age and gender
  - 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

## Statistics

- Cohen's d was used to express the magnitude of the difference between groups as an effect size.<sup>5</sup> By convention, the magnitude of the Cohen's d value can be considered small=0.2, medium=0.5 and large=0.8

## 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 a memory impairment on either the ISLT learning score, the ISLT delayed recall score or both (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%)

Figure 3. Rate of impairment\* detected using ISLT

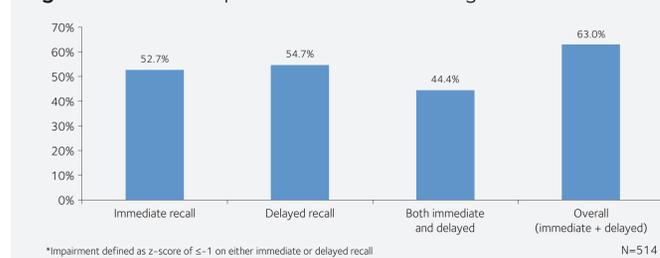
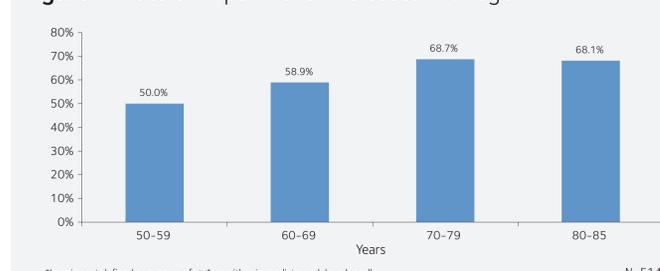
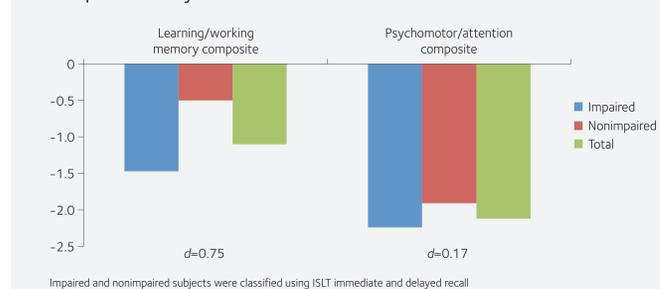


Figure 4. Rate of impairment\* increases with age



- Comparison of CBB performance between impaired and nonimpaired groups, as determined by the ISLT, indicated that the impaired group showed a large deficit on the Cogstate One Back Test ( $d=0.64$ ), One Card Learning Test ( $d=0.70$ ), and consequently on the learning/working memory composite ( $d=0.75$ ) (Figure 5)
- There was no impairment on the Detection Test ( $d=0.22$ ), Identification Test ( $d=0.14$ ), or psychomotor/attention composite ( $d=0.17$ )
- Agreement between classification of impairment on the ISLT and classification of impairment on the CBB was 66.1%

Figure 5. Comparison of performance on CBB and impaired and nonimpaired subjects



## 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

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