The Coalition Against Major Diseases: Towards U.S. FDA Qualification of Hippocampal Volume as a Biomarker for Enrichment in Clinical Trials for Pre-dementia Stages of Alzheimer disease

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Background

- The development of drugs for pre-dementia stages of Alzheimer disease (AD) poses the challenge of patient heterogeneity in clinical trials (Ref. 1).
- Trial enrichment via prognostic biomarkers provides one means of addressing such a challenge (Ref. 2).
- Hippocampal atrophy is associated with progression from pre-dementia to dementia and may help with trial enrichment.

Objectives

- To obtain regulatory qualification of baseline intracranial volume-adjusted hippocampal volume (ICV-HV) as an enrichment biomarker in pre-dementia trials, via a quantitative disease progression model.

Methods

- Individual-level data from three studies – the Alzheimer’s Disease Neuroimaging Initiative (ADNI)-1 and ADNI-2 observational studies (Ref. 3), and the Investigation Into Delay to Diagnosis of Alzheimer’s Disease With Exelon (InDDeX) clinical trial (Ref. 4) – have been integrated using the Clinical Data Interchange Standards Consortium (CDISC) therapeutic-area standards for AD.
- Volumetric magnetic resonance imaging (vMRI) data re-processed, and ICV-HV determined by the LEAP™ and FreeSurfer™ algorithms.
- Briefing documents and face-to-face meetings have been held with the U.S. Food and Drug Administration (FDA) to finalize the proposed context-of-use statement and the statistical analysis plan.

Results

- The proposed context-of-use statement and endpoint is summarized in Box 1.
- The analysis dataset, consisting of pre-dementia patient-level data from ADNI-1, ADNI-2 and InDDeX, has been standardized and curated. Preliminary summary statistics are presented in Table 1.
- The temporal trajectory of Clinical Dementia Rating – Sum of Boxes (CDR-SB) will be described by a mixed-effects statistical model, in which other covariates besides ICV-HV will be included (Figure 1).
- Monte Carlo clinical trial simulations will compare the statistical power by sample size in trials with and without ICV-HV enrichment, and a user-friendly graphical user interface will be developed.
- The full qualification document will be submitted to the FDA by 4Q-2017.

Target Population: Patients with amnestic mild cognitive impairment

Mini-mental State Examination (MMSE) scores between 24-30 (inclusive), a memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia (ADNI criteria).

Intended Application:

Clinical trial enrichment for pre-dementia Phase II and Phase III studies, based on the prognostic imaging biomarker ICV-HV as a predictor of disease progression.

Endpoint:

Clinical Dementia Rating Scale Sum-of-Boxes CDR-SB.

Box 1: Summarized Context-of-Use and Endpoint

Table 1 Summary of Baseline Individual Characteristics (N=1132)

<table>
<thead>
<tr>
<th>Baseline*</th>
<th>ADNI-1</th>
<th>ADNI-2</th>
<th>InDDeX</th>
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<tbody>
<tr>
<td>Sample size</td>
<td>397</td>
<td>341</td>
<td>394</td>
</tr>
<tr>
<td>MCI stage (%)</td>
<td>Late (100)</td>
<td>Early (52), Late (48)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Female (36), Male (64)</td>
<td>Female (45), Male (55)</td>
<td>Female (50), Male (50)</td>
</tr>
<tr>
<td>Age in year, mean (range)</td>
<td>74 (54, 89)</td>
<td>71 (55, 90)</td>
<td>70 (53, 89)</td>
</tr>
<tr>
<td>Number of APOE e4 alleles (%)</td>
<td>0 (47), 1 (42), 2 (12)</td>
<td>0 (40), 1 (39), 2 (11), Missing (1)</td>
<td>Missing (100)</td>
</tr>
<tr>
<td>Amyloid-beta imaging (%)</td>
<td>Negative (2), Positive (2), Missing (96)</td>
<td>Negative (40), Positive (57), Missing (3)</td>
<td>Missing (100)</td>
</tr>
<tr>
<td>ICV-HV in mm3, mean (range)**</td>
<td>5112 (2337, 7665)</td>
<td>5498 (3128, 8422)</td>
<td>5637 (3490, 7707)</td>
</tr>
<tr>
<td>CDR-SB, mean (range)***</td>
<td>1.6 (0.5)</td>
<td>1.5 (0.5, 5.5)</td>
<td>1.4 (0.5, 4)</td>
</tr>
</tbody>
</table>

* In ADNI, sample sizes and baseline characteristics are presented according to the study that the individual was first enrolled.
** ICV-HV were determined using the LEAP™ algorithm.
*** CDR-SB scores were assessed at the screening visit.

Conclusion

- This ongoing biomarker qualification effort with the FDA highlights the importance of understanding disease progression quantitatively to support the qualification of ICV-HV for prognostic purposes.
- If ICV-HV demonstrates utility in clinical trial enrichment, qualification of this biomarker can streamline drug development programs in AD by insuring the right patients are enrolled into our trials.

References