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**

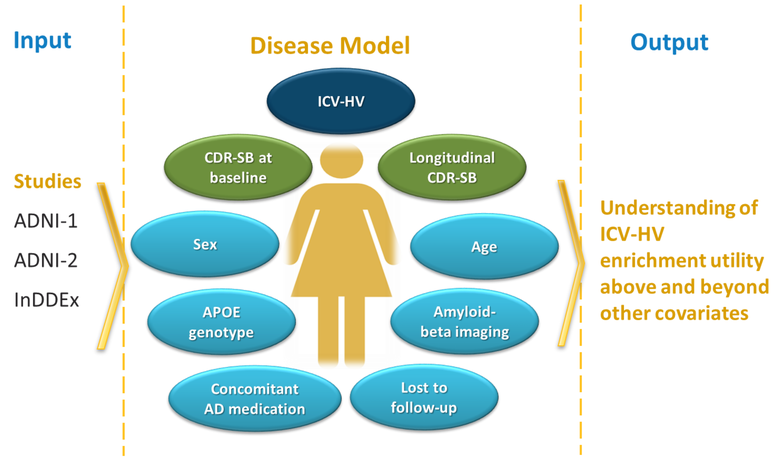

Figure 1 **Schematic of the Model-Informed Biomarker Enrichment Analysis**

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

Baseline*	ADNI-1	ADNI-2	InDDEx
Sample size	397	341	394
MCI stage (%)	Late (100)	Early (52), Late (48)	Not specified
Sex (%)	Female (36), Male (64)	Female (45), Male (55)	Female (50), Male (50)
Age in year, mean (range)	74 (54, 89)	71 (55, 90)	70 (53, 89)
Number of APOE e4 alleles (%)	0 (47), 1 (42), 2 (12)	0 (49), 1 (39), 2 (11), Missing (1)	Missing (100)
Amyloid-beta imaging (%)	Negative (2), Positive (2), Missing (96)	Negative (40), Positive (57), Missing (3)	Missing (100)
ICV-HV in mm^3, mean (range)**	5112 (3237, 7665)	5498 (3128, 8422)	5637 (3490, 7707)
CDR-SB, mean (range)***	1.6 (0, 5)	1.5 (0.5, 5.5)	1.4 (0.5, 4)

* 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

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Acknowledgments: This work was supported by a grant the Arizona Alzheimer's Consortium and, in part, by grant number 1U18FD005320 from the U.S. Food and Drug Administration's Critical Path Public Private Partnerships Grant, and members including: AbbVie Inc., Alzheimer's Association, Alzheimer's Disease Discovery Foundation, Alzheimer's Research UK, Biogen, Boehringer Ingelheim, CHDI Foundation, Eisai, Eli Lilly, F. Hoffmann La Roche, Merck Sharp & Dohme, Novartis Pharmaceuticals Corporation, Pfizer Inc., Takeda Pharmaceuticals, and UsAgainstAlzheimer's.