FDA Qualification of Intracranial Adjusted Hippocampal Volumetric Magnetic Resonance Imaging as a Prognostic Biomarker for Pre-Dementia Clinical Trials for Alzheimer Disease Therapeutics

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Background

- Disease-modifying/preventative treatments for Alzheimer disease (AD) are expected to be most effective at early disease stages.
- Early stage selection of the right subjects is challenging due to pathophysiological uncertainty or patient heterogeneity.
- In 2011, the EMA concluded that hippocampal atrophy, measured by volumetric magnetic resonance imaging (vMRI) and considered as a dichotomized variable, appears to help enriching recruitment into pre-dementia clinical trials (**Ref. 1**).

Objectives

- The Coalition Against Major Diseases (CAMD), a consortium within the Critical Path Institute, aims to obtain FDA qualification of intracranial adjusted hippocampal volume vMRI (ICV-HV vMRI; **Figure 1**) as an enrichment biomarker for pre-dementia clinical trials.
- The work herein describes the pathway to submit an ICV-HV vMRI qualification dossier to FDA in late 2017.

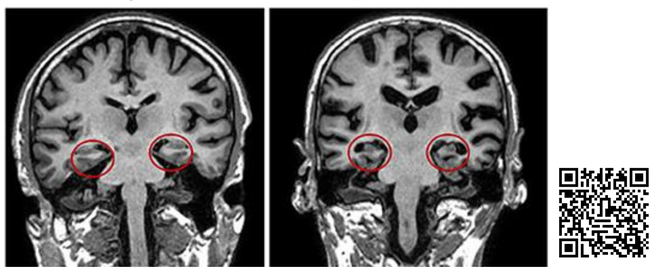

Figure 1. Hippocampal volume magnetic resonance imaging

Methods

- Formal meetings have been held with the FDA to finalize the context-of-use statement for ICV-HV vMRI as a prognostic enrichment biomarker, as well as the statistical analysis plan.
- The Alzheimer's Disease Neuroimaging Initiative (ADNI)-1 and ADNI-2 observational studies, and the Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon (InDDEx) clinical trial were standardized to the Clinical Data Interchange Standards Consortium (CDISC) AD therapeutic-area standards.

Results

Context of Use

- The summarized context of use is presented in **Box 1**.

Data

- Integrated, individual-level, longitudinal, CDISC-standardized dataset consisting of more than 1,000 MCI subjects from the ADNI-1, ADNI-2 and InDDEx studies (**Table 1**).

ICV-HV vMRI Images

- The vMRI images have been reprocessed with ICV-HV vMRI determined using LEAP™ and FreeSurfer™ algorithms.

Results (cont.)

Box 1 **Summarized Context-of-Use**

Target Population: subjects with mild cognitive impairment (MCI)

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 Clinical Dementia Rating (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).

Stage of Drug Development

Phase II and III stages of clinical drug development in MCI, including proof-of-concept, dose-ranging, early efficacy and safety clinical studies through clinical trials for registration of a therapy for pre-dementia.

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.

Table 1 **Baseline characteristics by study (total sample size = 1051)**

Baseline	ADNI-1	ADNI-2	InDDEx
Sample size	381	321 *4	349
Group names (%)	'Late MCI' (100)	'Early MCI' (52), 'Late MCI' (48)	'MCI'
Sex (%)	Female (36), Male (64)	Female (44), Male (56)	Female (47), Male (53)
Age in year, median (range)	75 (55, 89)	72 (55, 90)	71 (53, 89)
Body mass index in kg/m^2, median (range)	26 (18, 41)	27 (17, 51)	Missing
Number of APOE ε4 alleles (%)	0 (46), 1 (42), 2 (12)	0 (49), 1 (40), 2 (12)	Missing
Amyloid beta positive (%) *1	No (2), Yes (2), Missing (96)	No (40), Yes (59), Missing (1)	Missing
ICV-HV in mm^3, median (range) *2	5056 (3237, 7665) [Missing for 88 subjects or 23%]	5459 (3128, 8422) [Missing for 62 subjects or 19%]	5692 (3490, 7707) [Missing for 233 subjects or 67%]
CDR-SB, median (range) *3	1.5 (0.5, 5)	1.5 (0.5, 4.5)	1.0 (0.5, 3.5)
CDR-SB, mode	1.0	0.5	1.0
MMSE, median (range)	27 (24, 30)	28 (24, 30)	28 (24, 30)
Dropout by the 48-month visit (%)	No (58), Yes (42)	No (77), Yes (23)	No (66), Yes (34) *5
Subject follow-up duration in months, median (range)	36 (5.1, 58)	37 (4.7, 53)	38 (0.46, 50)

Notes: Proportions not adding up to 100% are due to rounding. *1 Amyloid beta positivity was determined by PET imaging; *2 ICV-HV was determined using the LEAP algorithm; *3 CDR-SB assessment were performed at screening. *4 There were 16 subjects who transitioned from ADNI-1 to ADNI-2 and were accounted for in ADNI-1 but not in ADNI-2 to prevent double counting; *5 InDDEx subjects with CDR-SB scores at the 48-month visit were considered completers.

Acronyms: MCI = mild cognitive impairment, ICV-HV = intracranial volume-adjusted hippocampal volume, CDR-SB = clinical dementia rating scale – sum of boxes, MMSE = mini-mental state examination, ADNI = Alzheimer's Disease Neuroimaging Initiative, InDDEx = Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon.

Ref. 1. Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials - in pre-dementia stage of Alzheimer's disease.

Results (cont.)

Endpoint

- The model endpoint is the Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB), as per FDA feedback.

Statistical Analysis

- The trajectory of CDR-SB over time will be described by a mixed-effects statistical model, which allows the differentiation of sources of variability.
- Along with baseline ICV-HV vMRI, sex, baseline disease severity, baseline age, and apolipoprotein E genotype will be included as covariates.
- Utility of ICV-HV vMRI enrichment will be compared between LEAP™ and FreeSurfer™ algorithms.
- Enrichment utility will be determined by several analysis outputs, including whether simulated biomarker-enriched trials have increased statistical power to demonstrate a drug effect of reduction in progression rate.

Preliminary Results on Enrichment Utility

- Baseline ICV-HV vMRI values linearly related to the rate of CDR-SB progression in a model adjusted by age, sex, mini-mental state examination, and APOE ε4 genotype, . For each 1 cm^3 decrease in the ICV-HV, the progression rate was estimated to increase by 88% (95% CI: 47%, 130%) (**Figure 2**).
- As an example, ICV-HV enrichment (inclusion of subjects with baseline ICV-HV < 5.25 cm^3) allowed a sample size per arm of ~250 (vs. ~500 without enrichment) in a 2-year parallel study to detect a drug effect of 50% reduction in rate with 80% probability at α=0.05 (N=3000 Monte Carlo based clinical trial simulations).

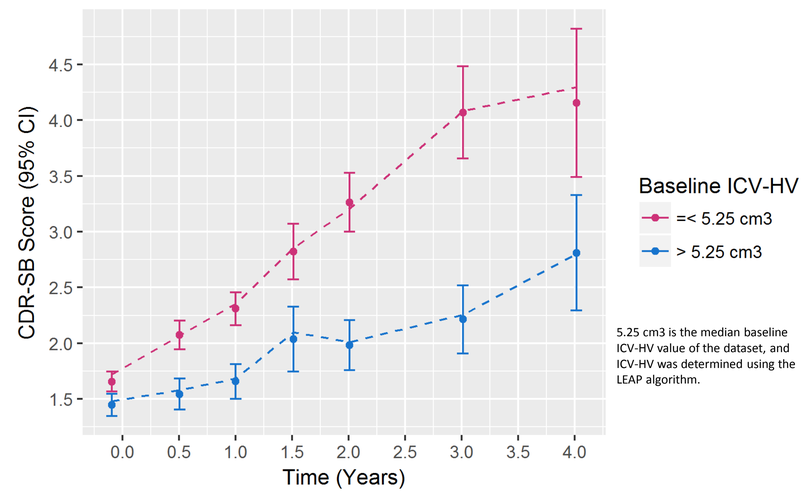

Figure 2. Mean CDR-SB scores stratified by baseline ICV-HV vMRI in ADNI-1 and ADNI-2. Dots are observed scores with 95% confidence intervals (CI) and dashed lines are model predictions.

Conclusions

- Further exploration of imaging technologies for prognostic biomarker purposes should be encouraged.
- Having frequent dialogue with regulators is critical to shape the development, validation, and clinical relevance of drug development tools.
- Model-informed enrichment analyses can streamline the pathway towards regulatory biomarker qualification.
- If ICV-HV vMRI enrichment utility is confirmed, its qualification with the FDA will increase the efficiency of clinical trial design and pre-dementia drug development programs for AD in the United States.

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