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.

Results (cont.)

Summarized Context-of-Use Box 1

Target Population: subjects with mild cognitive impairment (MCI)

(inclusive), a memory complaint, objective memory loss measured

Mini-mental State Examination (MMSE) scores between 24-30

Results (cont.)

Endpoint

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

CRITICAL PATH

- 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

- Coalition Against Major Diseases (CAMD), a The 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.

Healthy Control



Mild Cognitive Impairment



- III MARA III

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.

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

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) <i>,</i> Male (64)	Female (44), Male (56)	Female (47), Male (53)			
Age in year, median (range)	75 (55, 89)	72 (55, 90)	71 (53 <i>,</i> 89)			
Body mass index in kg/m ² , median (range)	26 (18, 41)	27 (17, 51)	Missing			
Number of APOE ε 4 alleles (%)	0 (46), 1 (42), 2 (12)	0 (49) <i>,</i> 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)			

Statistical Analysis

- The trajectory of CDR-SB over time will be described by a mixedeffects 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 ε 4 genotype, . For each 1 cm³ decrease in the ICV-HV, the progression rate was estimated to increase by 88% (95%) Cl: 47%, 130%) (Figure 2).
- As an example, ICV-HV enrichment (inclusion of subjects with baseline ICV-HV < 5.25 cm³) allowed a sample size per arm of \sim 250 (vs. \sim 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).

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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
- individual-level, longitudinal, CDISC-Integrated, standardized dataset consisting of more than 1,000 MCI

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.

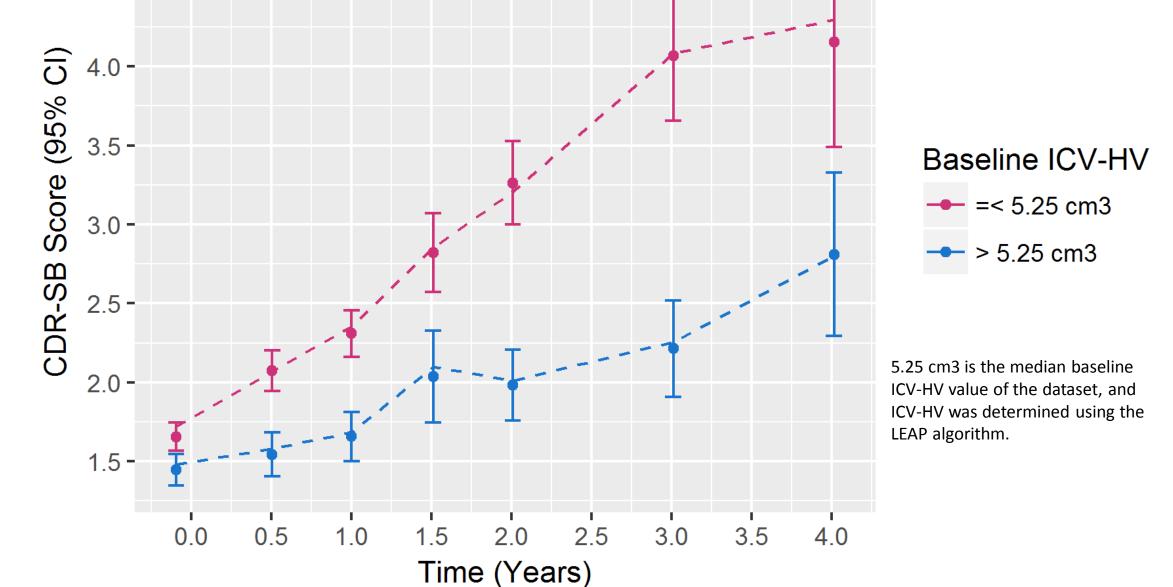


Figure 2. Mean CDR-SB scores stratified by baseline ICV-HV vMRI in **ADNI-1 and ADNI-2.** Dots are observed scores with 95% confidence intervals (CI) and dashed lines are model predictions.

Conclusions

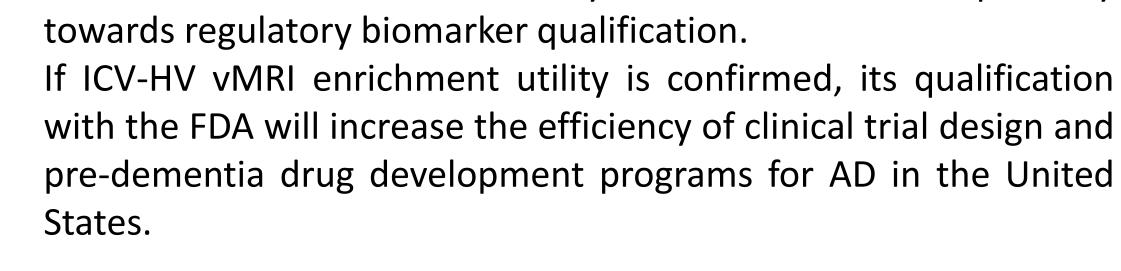
- Further exploration of imaging technologies for prognostic biomarker purposes should be encouraged.
- Having frequent dialogue with regulators is critical to shape the development, validation, and clinical relevance of drug development tools.
- Model-informed enrichment analyses can streamline the pathway

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.

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.



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