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

Daniela J. Conrado, PhD, Klaus Romero, MS, MD, Derek L. Hill, PhD, Patricia E. Cole, MD, PhD, Dawn Matthews, PhD, Gerald Novak, MD, Volker D. Kern, PhD, Robin Wolz, PhD, Richard Meibach, PhD, Jackson Burton, PhD, Brian Corrigan, PhD, Timothy Nicholas, PhD, Danny Chen, PhD, Julie Stone, PhD, Vikram Sinha, PhD, Brian Willis, PhD, Wenping Wang, PhD, Stephen P. Arnerić, PhD

(1) Critical Path Institute, Tucson, AZ, USA; (2) IXICO, London, United Kingdom; (3) Cole Imaging and Biomarker Consulting LLC, Glenview, IL, USA; (4) ADMDX, Chicago, IL, USA; (5) Janssen Pharmaceuticals (J&J), Titusville, NJ, USA; (6) Novartis, NJ, USA; (7) Pfizer Inc, Groton, CT, USA; (8) Merck, West Point, PA, USA; (9) Eli Lilly, Indianapolis, IN, USA

Background

- Disease-modifying/preventive 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.

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 trial design 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)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>ADNI-1</th>
<th>ADNI-2</th>
<th>InDDEx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>381</td>
<td>321 **</td>
<td>349</td>
</tr>
<tr>
<td>Group names (%)</td>
<td>Late MCI (100)</td>
<td>Early MCI (52), Late MCI (48)</td>
<td>MCI</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Female (36), Male (64)</td>
<td>Female (44), Male (56)</td>
<td>Female (47), Male (53)</td>
</tr>
<tr>
<td>Age in year, median (range)</td>
<td>77 (55, 89)</td>
<td>72 (55, 90)</td>
<td>71 (53, 89)</td>
</tr>
<tr>
<td>Body mass index in kg/m², median (range)</td>
<td>26 (18, 41)</td>
<td>27 (17, 51)</td>
<td>Missing</td>
</tr>
<tr>
<td>Number of APOE ε4 alleles (%)</td>
<td>0 (46), 1 (42), 2 (12)</td>
<td>0 (49), 1 (40), 2 (12)</td>
<td>Missing</td>
</tr>
<tr>
<td>Amyloid beta positive (%) *</td>
<td>No (2), Yes (2), Missing (96)</td>
<td>No (40), Yes (59), Missing (1)</td>
<td>Missing</td>
</tr>
<tr>
<td>ICV-HV in cm³, median (range) **</td>
<td>5056 (3237, 7665)</td>
<td>5459 (3128, 8422)</td>
<td>5692 (3490, 7707)</td>
</tr>
<tr>
<td>CDRSB, median (range) **</td>
<td>1.5 (0.5, 5)</td>
<td>1.5 (0.5, 5)</td>
<td>1.0 (0.5, 3.5)</td>
</tr>
<tr>
<td>MMSE, median (range)</td>
<td>27 (24, 30)</td>
<td>28 (24, 30)</td>
<td>28 (24, 30)</td>
</tr>
<tr>
<td>Dropout by the 48-month visit (%)</td>
<td>No (58), Yes (42)</td>
<td>No (77), Yes (23)</td>
<td>No (66), Yes (34) *</td>
</tr>
<tr>
<td>Subject follow-up duration in months, median (range)</td>
<td>36 (5, 158)</td>
<td>34 (7, 47, 53)</td>
<td>38 (0.46, 50)</td>
</tr>
</tbody>
</table>

Notes: Proportions not adding up to 100% are due to rounding. * Amyloid beta positivity was determined by PET imaging. ** ICV-HV was determined using the LEAP algorithm. CDR-SB assessment were performed at screening. * 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. ** CDR-SB scores at the 48-month visit were considered complete.

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.

Acknowledgments: This work was supported, in part, by grant number U1USD905320 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 Drug Discovery Foundation, Alzheimer’s Research UK, Biogen, Boehringer Ingelheim, CHDI Foundation, Eisai, F. Hoffmann La Roche, Janssen, Eli Lilly and Company, Merck Sharp & Dohme, Novartis Pharmaceuticals Corporation, Pfizer Inc., Takeda Pharmaceuticals, and UsAgainst Alzheimer’s.

Figure 1. Hippocampal volume magnetic resonance imaging

Figure 2. Mean CDR-SB scores stratified by baseline ICV-HV vMRI in ADNI-1 and ADNI-2.

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 cm³ 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 cm³) 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).

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 reproposed with ICV-HV vMRI determined using LEAP™ and FreeSurfer™ algorithms.

Figure 1. Healthy Control and Mild Cognitive Impairment

Figure 2. Mean CDR-SB scores stratified by baseline ICV-HV vMRI in ADNI-1 and ADNI-2.