CAMD & FDA 2015 Annual Scientific Workshop
Alzheimer’s Disease CSF Biomarker Working Group

October 15, 2015 / FDA White Oak Campus
AD CSF Biomarker Project Team

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University of Pennsylvania—Les Shaw
ADNI: Biomarker & clinical change in late onset disease

Model provides biological rationale for potential prognostic uses of CSF biomarkers to enrich trials for risk for progression and subsequent conversion

Modified from Jack et al 2013
AD CSF Biomarker – Current Status

• Extensive scientific literature reports that cerebrospinal fluid (CSF) biomarkers including $A\beta_{1-42}$, total Tau and/or phospho-Tau reliably identify individuals in pre-dementia trials likely to progress to AD dementia

• Basis for EMA qualification of CSF $A\beta_{1-42}$ and total Tau for this use

• FDA has accepted sponsor-specific CSF biomarker-based proposals for this use

• FDA has yet to qualify CSF biomarkers for this use
AD CSF Biomarker - Project Objective & Impact

Objective

• Advance through the formal FDA regulatory biomarker qualification path the use of CSF Aβ_{1-42}, total tau and/or phospho-tau in conjunction with clinical assessments to enrich pre-dementia trials for individuals likely to progress

Focus

• The enrichment of trials based on the proposed approach is intended to be applied across a range of molecular targets and clinical trial designs sponsored by our stakeholders

• The focus on multiple CSF biomarkers is based on the concern that single biomarkers may not be sufficient to optimize clinical trial enrichment across the diversity of molecular targets, pathology, populations and clinical stage of interest to the sponsors
Pathways to integrate biomarkers in drug development

Objective: Use the biomarker in a single drug development program

Acceptance through IND, NDA and BLA submissions (Drug approval process)

• Responsible Parties: One sponsor contacts the review division
• Process: Discuss, provide rationale and data to the review division
• Risk and resource: burden on one sponsor
• Biomarker Information: Embedded in drug labels

Objective: Establish the biomarker for use in multiple development programs

Biomarker Qualification

• Responsible Parties: Generally, consortia contact the BQ Program
• Process: Submit letter of intent. Follow the BQ process
• Risk and resources: shared among consortia members
• Biomarker Information: qualified biomarkers announced as draft guidance

Scientific Evidence supports AD CSF biomarkers for Prognostic Use

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Abnormal CSF Aβ</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heister D</td>
<td>2011</td>
<td></td>
<td>3.40 (1.70, 6.90)</td>
<td>32.92</td>
</tr>
<tr>
<td>McEvoy L</td>
<td>2011</td>
<td></td>
<td>3.68 (1.89, 7.92)</td>
<td>32.65</td>
</tr>
<tr>
<td>van Rossum IA</td>
<td>2012</td>
<td></td>
<td>0.90 (0.50, 1.70)</td>
<td>34.43</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>2.21 (0.87, 5.63)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal CSF p-tau</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landau SM</td>
<td>2010</td>
<td>2.88 (1.09, 7.59)</td>
<td>13.59</td>
</tr>
<tr>
<td>Heister D</td>
<td>2011</td>
<td>2.90 (1.60, 5.30)</td>
<td>35.67</td>
</tr>
<tr>
<td>van Rossum IA</td>
<td>2012</td>
<td>3.60 (1.30, 9.20)</td>
<td>13.36</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.490)</td>
<td></td>
<td>2.43 (1.70, 3.48)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal CSF I-tau</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heister D</td>
<td>2011</td>
<td>1.80 (1.10, 2.70)</td>
<td>50.25</td>
</tr>
<tr>
<td>van Rossum IA</td>
<td>2012</td>
<td>2.30 (1.10, 4.60)</td>
<td>19.79</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.798)</td>
<td></td>
<td>1.86 (1.35, 2.55)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal CSF tau/A-beta 1–42</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landau SM</td>
<td>2010</td>
<td>3.99 (1.19, 13.32)</td>
<td>13.13</td>
</tr>
<tr>
<td>Heister D</td>
<td>2011</td>
<td>3.80 (1.80, 8.20)</td>
<td>20.62</td>
</tr>
<tr>
<td>McEvoy L</td>
<td>2011</td>
<td>3.68 (1.89, 7.92)</td>
<td>23.09</td>
</tr>
<tr>
<td>Gomar JJ</td>
<td>2014</td>
<td>2.34 (1.45, 3.91)</td>
<td>46.17</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.601)</td>
<td></td>
<td>3.00 (2.12, 4.23)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Forest plot shows the association between demographic features and the risk of progression from MCI to AD (AD, Alzheimer’s disease; MCI, mild cognitive impairment; RR, relative risk).

Li et al., BMJ 2015
Biomarker-based diagnosis embedded in 2011 NIA-AA research criteria for MCI due to AD

The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging and Alzheimer’s Association workgroup

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

Table 3
MCI criteria incorporating biomarkers

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI—core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/untested</td>
</tr>
<tr>
<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</td>
</tr>
<tr>
<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Untested</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

Albert M et al. (2011) Alzheimers & Dementia
Proposed Context-of-Use for AD CSF Biomarkers

• **Biomarker Analyte(s):** CSF Aβ₁₋₄₂, tau and/or phospho-tau

• **Biomarker Application:** Prognostic enrichment

• **Target Population:** Patients with amnestic mild cognitive impairment (aMCI)
  - MMSE scores between 24-30 (inclusive)
  - Subjective memory complaint
  - Objective memory loss by education adjusted Wechsler Memory Scale Logical Memory II
  - CDR of 0.5
  - Absence of significant levels of impairment in other cognitive domains
  - Essentially preserved activities of daily living
  - Absence of dementia (ADNI criteria)

• **Context-of-Use:** The proposed use for CSF analytes is for enrichment purposes based on inclusion in a clinical trial. The rationale is to target patients with early AD (aMCI specifically) more likely to show cognitive and functional decline during the course of a clinical trial
Method-Related Sources of Variability

Pre-Analytical
- Patient status
- Patient medications
- Patient preparation
- Sample collection
- Sample handling

Analytical
- Assay components & format (manufacturer & laboratory)
  - Instrument technology & performance
  - Reagents: Source, quality, characteristics, stability
  - Antibody epitope, affinity, cross reactivity, purity, stability
  - Calibrators (buffer) & Controls (buffer & native matrix based)
- Assay procedure (manufacturer & laboratory)
- Assay validation – documented performance
  - Accuracy based methods are ideal but not essential for clinical utility
  - Precision-based methods have established clinical utility in both intra- & inter-lab settings
  - Longitudinal stability – External proficiency
- Analyst – competent & qualified to perform the assay

Post-Analytical
- Data processing
  - Hardware & software validation
  - Calibration model
  - Lab specific QC/QA
  - Run & result rejection criteria
  - Cut point determination for converting continuous numerical data to clinically-relevant categorical results

Analytical Stability: Time & Reagent Lot

Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI

Leslie M. Shaw · Hugo Vanderstichele · Małgorzata Knapik-Czajka · Michal Flgurski · Els Coart · Kaj Bienow · Holly Soares · Adam J. Simon · Piotr Lewczuk · Robert A. Dean · Eric Siemons · William Potter · Virginia M.-Y. Lee · John Q. Trojanowski · the Alzheimer’s Disease Neuroimaging Initiative

Fig. 5A

Aβ<sub>1-42</sub> Test/Re-test Correlation
Yet to be published commutability study demonstrated neat CSF CRM can be used for value assignment of most Aβ42 methods.
Evidentiary Standards for Analytical Validation
Cross Consortia Initiative for Assay Expectations for BM Qualification

Goal

• Define a standard set of scientific and regulatory expectations for the validation of biomarker assays from early biomarker discovery through qualification and implementation

Objectives

• Define the rationale underpinning scientific expectations for assay validation to be used for biomarker qualification with industry stakeholder
• After gaining stakeholder alignment, work towards gaining support of the approach with both FDA and EMA
• Utilize publications and workshops to reach broader consensus and ultimately propose guidance on progressive assay validation

CAMD: Johan Luthman, Hugo Vanderstichele, Bob Dean, Alvydas Mikulskis
C-Path: Amanda Baker, Nick King, Volker Kern, Diane Stephenson, John Michael Sauer, Steve Arneric
PSTC: Steve Piccoli, Shelli Shoumaker
SAFE-T: Thomas Joos, Thomas Schindler, Thomas Knorpp
AAPS: Ron Bowsher, Bill Nowaske
Thank you for your participation in the Evidentiary Considerations for Integration of Biomarkers in Drug Development Symposium.

A recording of the Symposium and presentations are available now:

Co-Sponsored by:
The University of Maryland CERSI, U.S. FDA, and Critical Path Institute

Federal Register Notice posted:
https://federalregister.gov/a/2015-19037

Goal: Begin to define and ultimately codify scientific and regulatory expectations for biomarker qualification
Evidentiary Standards tied to benefit / risk
A Prototypical Process for Creating Evidentiary Standards for Biomarkers and Diagnostics

CA Altar, D Amakye, D Bounos, J Bloom, G Clack, R Dean, V Devanarayan, D Fu, S Furlong, L Hinman, C Girman, C Lathia, L Lesko, S Madani, J Mayne, J Meyer, D Raunig, P Sager, SA Williams, P Wong, and K Zerba

A framework for developing evidentiary standards for qualification of biomarkers is a key need identified in the Food and Drug Administration’s Critical Path Initiative. This article describes a systematic framework that was developed by Pharmaceutical Research and Manufacturers of America (PhRMA) committees and tested at a workshop in collaboration with the Food and Drug Administration and academia. With some necessary refinements, this could be applied to create an appropriately individualized evidentiary standard for any biomarker purpose.
CHALLENGES: Major

• CSF collection: Cultural & professional acceptance

• Industry and academic trials often do not...
  - Use consistent clinical screening / inclusion criteria
  - Use consistent clinical follow-up assessments
  - Use consistent analytical biomarker methods
  - Study “negative” biomarker cohort (Excluded)
  - Obtain consent to share individual subject clinical & biomarker data
  - Obtain consent to share individual stored specimens

• Access to clinical trial data beyond ADNI:
  - BMS Avagacestat
  - DESCRIPA
  - Washington University ADRC, and
  - more...
• Appropriate relative to the proposed Context of Use
• Population similar to ADNI-1 and ADNI-2
• Same analytical approach to ADNI-1 and ADNI-2
CHALLENGES: Minor & More Manageable

• Adopt CDISC Standards
• Analytical & Interpretive
  - Short term: Control variability in reference labs as with other high complexity methods (Method-specific cut point)
  - Long term: Eliminate key sources of variability (Adopt universal cut point)
• Statistical Plan - Consensus
  - Focus of fewer analytes and derived results
  - Establish strength of association with clinical outcomes
    • Initially retrospective / prospective (limited qualification)
    • Eventually prospective (expanded qualification)
  - Define generalizeability
We encourage the inclusion of these exploratory CSF biomarkers in clinical trials to evaluate their clinical utility for identifying patients likely to show clinical progression of their MCI symptoms for the purpose of clinical trial enrichment. We consider data collection on this biomarker to be exploratory in nature. When including these biomarkers in clinical trials, sponsors are encouraged to employ consensus AD CDISC\textsuperscript{2} standards for data harmonization. We believe that sharing and integrating data across trials can foster an accelerated path for AD drug development programs. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a given IND drug development program, they should prospectively discuss with the Division of Neurology Products in CDER.

Sincerely,

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration
FDA speaks out....What is Needed

- Enhanced data sharing and collaborative efforts among consortia
- **Focus:** Qualification packages that don’t try to “boil the ocean”
  - Limited vs Expanded Context of Use
- Data/specimen repositories which can support expanded contexts of use for biomarkers once additional data is aggregated
- Up front conversations around context of use—which drives the level of evidence needed
- More communication about the value and progress made by consortia efforts
- Greater clarity around levels of evidence for qualification—this takes the entire scientific community—not just FDA
- **Patience**...we are learning as we go...

Dr ShaAvrhee Buckman, Director, OTS
Contains Nonbinding Recommendations
Draft — Not for Implementation

Qualification of Biomarker—Plasma Fibrinogen in Studies Examining Exacerbations and/or All-Cause Mortality in Patients With Chronic Obstructive Pulmonary Disease

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (email: CDER-BiomarkerQualificationProgram@fda.hhs.gov).

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Plasma fibrinogen

Posted July 2, 2015
Paving the way for the future - promising biomarkers

Identifying Potential Biomarkers for Qualification and Describing Contexts of Use To Address Areas Important to Drug Development; Request for Comments

A Notice by the Food and Drug Administration on 02/13/2015

**ACTION** Notice; Request For Comments.

**CAMD biomarker teams submitted two candidate biomarkers:**
CSF Neurogranin (Kaj Blennow, Erik Portelius, Hugo Vanderstichele)
Tau PET imaging (Mike Weiner, Pat Cole, Susan DeSanti, Dawn Matthews, Jeff Sevigny)