The Potential use of Biomarkers in Alzheimer’s Disease in Different Stages of Drug Development

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Declaration of Conflict of Interest

I am a full time employee Eisai Inc.

I own shares in AstraZeneca and Merck Inc.
“Qualification and/or validation of a certain biomarker as diagnostic tools or as a surrogate endpoint is out of the scope of this document”

“May be outlined in detail in separate upcoming documents after EMA qualification processes (Ref. EMA/CHMP/SAWP/72894/2008)"


However, a the success of a new AD guideline will be intimately linked to acceptance of biomarker context of use and approval of biomarker products
Key considerations

- Biomarkers have emerged as essential for defining AD and staging of the disease along its spectrum
- Biomarkers are critical to support AD drug development
- Several AD biomarkers are available - with different, but also commonly overlapping applications
  - Alternative biomarker modalities
  - Interchangeable use of concordant biomarker modalities
- Variable degree of assay validation & clinical qualification
  - Which biomarker is fit for purpose in sponsor trials?
  - Which biomarkers may gain regulatory acceptance?
  - Which biomarkers will become generally used?
Early Development - Drug Mechanism Readout

Clinical Go/No-Go tests of molecules or hypotheses

**Proof of Presence**
Drug reaches target organ and/or shows Target Engagement (TE)

**Proof of Mechanism (PoM)**
Pharmacodynamic (PD) readout

- CSF Aβ peptide species lowering
- Molecular PET for TE
- Micro-dosing (AMS)

**Proof of Principle (PoP)**
PD effect on pathophysiology
- Brain Amyloid lowering (amyloid mAb)
- Brain Tau lowering (tau therapies)

- Also called PoC Lite

**Proof of Concept (PoC)**
Effect on disease

- Requires large studies using clinical outcome measures
- No surrogate outcome biomarkers

Molecular Imaging - PET

$A\beta$ Species in CSF
Steps from Biomarker Identification to Diagnostic/Outcome Measure

**Biomarker Identification**
- Hypothesis driven or Un-biased
- Modality? / Invasive or Non-invasive?

**Exploratory Biomarker**
- Feasibility evaluation

**Early Development**
- Drug Mechanism Readout (TE/PD)

**Intended Use?**

**Late Development**
- Diagnostic / Outcome Measure

**Clinical Application**
- Stop-Go use

**Fit for Purpose Assay**
- Custom developed assay

**Assay Validation**
- Prototype to analytically validated reagent
- Assay manufacturing (e.g. kit)
- Assay Standardization & SoP Collection/Storage

**Clinical Qualification**
- Diagnostic (cut-point determination)
- Outcome measure (link COA)

**Regulatory Process**
- Approved Diagnostic
- Accepted Outcome measure

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Use of AD Biomarkers

**Diagnostic** – Determining diagnosis#
- Clinically well-established - MRI, EEG etc.
- Dominant mutations
- Supportive/exploratory - amyloid PET, CSF measures etc.

**Prognostic** – Determining course of illness#
- Dominant mutations
- Hippocampal atrophy - volumetric MRI
- *Amyloid PET imaging*
- *CSF Aβ peptides or Tau protein*

#Definition according “Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer’s disease and other dementias”. EMA/CHMP/539931/2014,
Role of Biomarkers in AD Diagnosis?

- Clinical phenotype – different diagnostic criteria
- Neuropathology – gold-standard in biomarker qualification
  …but obtained much later in disease and with increasing mixed pathologies

**Bridging clinical & neuropathology phenotypes**

**Clinical Phenotype**
- Mayo criteria 1999
- IWG criteria 2007
- NIA-AA criteria 2011
- IWG-2 criteria 2014

**Biomarker Phenotype**
- ApoE isotype
- Amyloid PET
- CSF Aβ42
- CSF Tau
- HCV MRI

**Neuropathology Phenotype**
- Amyloid plaques
- Inflammation
- Neurofibrillary tangles
- Neurodegeneration
AD Biomarkers Used in Drug Development

**Stratification** – Segmentation into predetermined categories
- Genetic: ApoE isotype
- *volumetric MRI* – hippocampal

**Enrichment** (Companion Diagnostics) – Entry criteria
- Amyloid PET imaging
- CSF Aβ_{42} or Tau/ Aβ ratio
- Genetic: ApoE isotype, Dominant mutations
- *volumetric MRI* – hippocampal

**Predictive** – Treatment effect / Outcome measure
- *volumetric MRI* – hippocampal
- *Cerebrospinal fluid total-tau or P-tau
- *FTG-PET*

**Predictive** – Safety assessment
- Molecule specific
- Target class related/General measures
- Amyloid Related Imaging Abnormalities (ARIA-E/H)
- Skin pigmentation
Biomarker Development

“Assay” Approval (“cleared assay”)
- Test performing measurement - “Assay Validation”
- Medical Device
  - Does not work via chemical action in the body
- IND / IMP
  - Works via chemical action in the body, e.g. PET ligand

“Context of Use”
- Purpose of measurement - “Clinical Qualification”
- Stand Alone - Not associated with specific drug treatment
  - “Gold standard” – standard of truth comparison to judge performance
- Companion Diagnostic - Identifies condition of drug use
  - Enrichment biomarkers

- Exploratory/Secondary Outcome Measure
  - Ultimate goal is Surrogate Outcome measure
EMA - Qualification of Novel Methodologies for Drug Development

- CSF Biomarkers (BMS) - Opinions April 2011 (MCI) & February 2012 (MM-AD)
  - Need for cut-point definition
- vMRI/Hippocampal Volume (CAMD) - Qualification opinion October 2011
- Amyloid PET (BMS) - Opinion February 2012 (PET and CSF for MM-AD)

FDA - Drug Development Tools (DDT) Qualification

- No AD Biomarker DDT qualification issued
  - CSF Biomarkers submitted (CAMD) November, 2011
  - vMRI/Hippocampal volume submitted (CAMD) April 21, 2011

Qualification requires a reliable measurement method, but it is conceptually independent of specific test
Biomarker Test Characteristics

**Cut-Point (Cut-off, Threshold) Determination**
- Requires extensive assay standardization & clinical qualification
- Cut-points for AD biomarkers
  - Amyloid PET – SUVR or Visual Read
  - CSF – pg/mL
  - vMRI/Hippocampal volume – cm³

**Performance Characteristics**
- Analytical performance
  - Assay stability & precision
  - Reproducibility
- Sensitivity & Specificity / Positive & Negative Predictive Values
  - Receiver Operating Characteristic Curve (ROC)
“Fluid” Biomarker Assay Maturity

FDA Terminology

- **Laboratory Developed Test (LDT, earlier called *homebrews*)**
  - Developed & used within one lab that offers testing service

- **Research Use Only (RUO)**
  - Not for diagnostic use – only for exploratory analysis

- **Investigational Use Only (IUO)**
  - Undergoing performance evaluation
    - Meet FDA criteria for Investigational Device Exemption (IDE)

- **In Vitro Diagnostic Medical Device (IVD)**
  - Diagnosis to cure, mitigate, treat, or prevent disease
    - Subject to EU IVD Director (98/79/EC)
    - Subject to FDA pre-market and post-market approval & controls
Europe – CE Mark

**Manufacturer's self-declaration**
- Verified by “Notified Body” (accredited to validate compliance)
- Not linked to Intended Use
- Permits products’ access to the market

**Companion Diagnostic (CoDx) - viewed as low risk**
- No need for Notified Body involvement
- Drug approval not required for device to be CE marked
- FDA - High risk” device (Class III; requiring Pre-Market Approval)

- Influence of revision of the EU regulation on In Vitro Diagnostic Medical Devices (IVD) on acceptability of stand-alone or companion AD biomarkers?
- Companion Diagnostic will be viewed as class C (high risk)

*Target for adoption Q2/3 2015*
Status Amyloid PET

- **Approved stand-alone ligands (FDA & EMA)**
  - Rule out presence of amyloid - not for AD “diagnosis”
  - Post mortem histopathology validation

- **Extensive use in “companion diagnostic” context**
  - Prodromal AD, Mild AD, Pre-symptomatic AD
  - Ongoing Reference standard project - the “Centiloid project”

- **Hampered by high entry barriers**
  - High costs & Reimbursement challenges
  - Complex infrastructure (cyclotron, distribution networks, PET centers)
  - Injection radioactivity – approval issues (German BfS)
Status CSF Biomarkers

* No approved Stand alone or Companion IVD
  * Commercialized RUO assays for Aβ42, Tau & P-tau (some CE marked)
  * Progression of Precision-based IVDs
  * Ongoing standardization
    * Reference Material and Methods (Accuracy-based assays)
      * “Global Consortium for the Standardization of CSF Biomarkers”
      * Initial focus on Aβ42 peptide

* Companion Diagnostic use in AD drug trials
  * Alone, or in sub-groups (supplement to Amyloid PET), using CE Mark / RUO assays

* Cultural/medical barriers for lumbar puncture
  * High acceptance Europe / Lower acceptance North America & Asia

* Supportive biomarker for disease modification claims
  * Tau or P-Tau – further clinical qualification needed
Inter-changeable Use of CSF Biomarkers & Amyloid PET for Enrichment

**EMA Discussion Paper:** “For the time being it’s not clear whether CSF and PET amyloid biomarkers are interchangeable…….”

Florbetapir Amyloid PET & CSF $A_\beta_{42}$ relationship

374 recently-recruited ADNI-GO/2 subjects

![Graph showing correlation between CSF $A_\beta_{42}$ and Florbetapir retention ratio](image)

ADNI-GO = Alzheimer’s Disease Neuroimaging Initiative - Grand Opportunity
CSF = Cerebrospinal fluid
MCI = Mild cognitive impairment
PET = Position emission tomography
1. Defined as cortical labeling (uptake of ligand) divided by cerebellum labeling.

- Concordance CSF/PET has consistently been shown to be $>85%$
- Key comparison **Visual Read on Amyloid PET & CSF assay cut point**
Hippocampal Volumetric (HCV) MRI as Diagnostic for MCI to AD Conversion

- Well established and early Qualification (EMA) for HCV-vMRI
  - Reasonable sensitivity / specificity

- Lower entry barriers c.f. CSF/Amyloid PET
  - High availability of clinical MRI, reasonable cost

- Low uptake for primary enrichment
  - Anti-amyloid therapy trials favor Amyloid PET or CSF Aβ42
  - vMRI concordance with other Biomarkers?
  - Stacking of biomarkers - further screening failure?

- High uptake as supportive Outcome measure (Disease Modification)
  - HCV remains to show effect in the “right” direction

Hill et al., Alzheimer’s & Dementia 10 (2014) 421–429
Other Emerging “Diagnostic” Biomarkers

**Tau PET Imaging**
- Ligands in development (patient studies)
- Potential to refine disease staging (Braak stages)
- Potential to re-define role of tau in early stage disease
- Potential to support clinical diagnosis (differential diagnosis)

**CSF Biomarkers (beyond Aβ and tau)**
- Oligomeric Aβ, TDP-43, VILIP1, NFL, α-synuclein (differential diagnosis) etc.

**Blood Biomarkers (beyond genetics/ApoE)**
- High potential, possible use as tier 1 profile biomarker
- Many kinds of analytes – single of multiplex
- Commonly high sensitivity, while challenges with specificity

**Retinal imaging**
- Development of high resolution/sensitive techniques - Optical Coherence tomography etc.
- Fluorescence imaging of amyloid

**Physiological tests**
- Olfactory function (hyposmia), pupillary diameter etc.
Key regulatory questions (1/3)

* Is the agency accepting that well established Research Use Only (RUO) CSF $A\beta_{42}$ assays can be used for “enrichment” in trials?

EFPIA believes that

* established RUO assays of $A\beta_{42}$ (Innotest $A\beta_{1-42}$ and Inno-BIA AlzBio3) have sufficient performance characteristics and adequately established cut points

  * Using centralized lab analysis

* established RUO $A\beta_{42}$ assays permit bridging to emerging Accuracy-based and IUO / IVD Precision-based assays

EMA Discussion paper: “it is strongly advised to measure not only $A\beta 1-42$ but also T-Tau or P-Tau levels…”

* EFPIA agrees that measuring Tau & p-tau is important as supportive predictive biomarkers

* Measurements of Tau species should not form the basis for trial enrichment until Accuracy-based or IUO assays are available for those analytes
Key regulatory questions (2/3)

EMA Discussion Paper: “For the time being it’s not clear whether CSF and PET amyloid biomarkers are interchangeable ………”

Could the agency revise its position and accept interchangeable use of biomarker products and modalities for “enrichment” of trial subjects?

EFPIA’s believes that

- amyloid biomarkers do no need additional within trial validation
  - available data support interchangeable use of approved Amyloid PET products
- Amyloid PET and CSF Biomarkers show sufficient concordance for either/or enrichment
  - without need for using PET and CSF in largely overlapping populations

EFPIA also proposes that the drug product Labeling language should reflect the pathology identified (evidence of amyloid pathology) rather than the specific biomarker modality used (e.g. Amyloid PET)
Key regulatory questions (3/3)

* Is the agency accepting bridging strategies for Standard of Truth validation of further “stand alone” diagnostics that identify a specific molecular pathology (e.g. amyloid pathology)?

EFPIA proposes that

* clinical and biomarker phenotypes are better suited as Standard of Truth for new biomarkers, if a high level of concordance is found between the new biomarker compared to an “established” biomarker (previously characterized using neuropathology data)

* sufficient data are available permitting using Amyloid PET as “standard of truth” for validation of CSFAβ$_{42}$ emerging CSF IVD products