Coalition Against Major Diseases

Regulatory Science can Accelerate Drug Development for Neurodegeneration

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Critical Path Institute

Collaborating for Cures – March 7, 2013- Brussels
After recent AD Phase III failures… What’s next?

Reasons for Phase III & Submission Failures: 2007-2010

- **Efficacy**: 66%
- **Safety**: 21%
- **Financial**: 7%
- **Not disclosed**: 6%

*Arrowsmith J. Nature Reviews Drug Discovery Feb 2011*
The Solution....Collaborations that enable ......

• Sharing knowledge
• Learning from failures
• Public-Private Partnerships
Our Knowledge of Alzheimer’s Disease has been Transformed through PPPs

- ADNI provided seminal new information concerning the pathophysiology of AD
- Defined early detection methods for identification of risk
- Improved treatment trials for assessing predictors and outcomes
- Accelerated a path leading to the treatment and prevention of AD

Biomarker staging of AD
The mission of CAMD is to advance innovative tools and technologies through a regulatory path that accelerates development of medical products for brain diseases.

Firsts:

• Therapeutic Area clinical data standards published by CDISC (AD and PD)
• Unified CDISC database of Alzheimer’s disease clinical trial information provided by multiple pharmaceutical companies
• Clinical trial modeling and simulation tool advanced for a regulatory decision
• Neuroimaging biomarker for Alzheimer’s Disease qualified by a regulatory agency (EMA)
CAMD: Tools to Advance Effective Treatments for Alzheimer’s and Parkinson’s Disease

Nonmember participants: Academic key opinion leaders, CROs
Alzheimer’s Disease-specific Therapeutic Area Supplement to the Study Data Tabulation Model User Guide

Prepared by the Coalition Against Major Diseases (CAMD)

Published Sept 2011
• Nine companies remapped and pooled data from 24 trials for ~6500 patients

• Database open to >200 qualified research teams in 35 countries
C-Path’s track record: Data and Modeling & Simulation tools
Biomarkers are being actively employed in AD therapeutic trials.

**Primary biomarkers**
- Amyloid PET
- CSF Aβ42
- CSF Aβ40
- CSF sAPPβ
- CSF BACE activity
- CSF Aβ1-14, Aβ1-15, Aβ1-16
- CSF sAPPα
- CSF Aβ oligomers

**Downstream biomarkers**
- CSF total tau
- MRI hippocampal volume
- CSF phospho-tau
- FDG PET

**Pathogenic process**
- Brain Aβ load
- γ-secretase-dependent APP and Aβ metabolism
- β-secretase-dependent APP and Aβ metabolism
- γ-secretase-independent APP and Aβ metabolism
- Aβ oligomerization
- Intensity of neuronal degeneration and brain atrophy rate
- Tau phosphorylation and tangles
- Brain glucose metabolism

**Position as theragnostic biomarker in trial type**
- Aβ immunotherapy
- BACE1 inhibitor
- γ-secretase inhibitor
- Aβ aggregation inhibitor

*Blennow, Nature Med 2010 16(11) 1218*
Biomarkers for Choosing the Right Patients

Baseline hippocampal volume

CSF biomarkers

**SLIDE 3**

Conceptual Model Depicting the Approach to Earlier Alzheimer’s Disease Diagnosis

- **Clinical Factors**
  - Episodic memory
  - Vascular risk factors
  - Depression

- **Biomarkers**
  - ApoE4 status
  - Structural imaging
  - CSF Aβ/tau/phosphotau
  - Functional imaging

MCI = mild cognitive impairment; AD = Alzheimer’s disease; ApoE4 = apolipoprotein E4; CSF = cerebrospinal fluid; Aβ = amyloid β.

*Feldman, CNS Spectr. 2008;13(3 Suppl 3):4-7*

Hansson et al., Lancet Neurol 5(3):228, 2006
Neuroimaging as a drug development tool for patient enrichment

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Agreed by Scientific Advice Working Party</td>
<td>1 September 2011</td>
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<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>22 September 2011</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>1 November 2011</td>
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CAMD Aligns with Relevant PPPs

Global Standardization Biomarkers Consortium

Alzheimer’s Prevention Initiative
Opportunity and Challenges

- Resource constraints at all levels
- Consortia fatigue
- Organizational Structure and Governance
- Data Sharing
- Communication among partners
- Culture
- Financing
- Incentives
- Risk Mitigation
- Respect for confidentiality
• Given the CAMD and IMI summaries of work-scope just presented do you see the gaps that are not being addressed, but would be critical to advancing the Alzheimer’s disease initiatives?

• What opportunities do you see for synergy/leveraging both efforts? Given the global scale of this disease we all agree that information and data "sharing" is critical. (Whether it is sharing across companies or PPP's).

• Do you view sharing of information as a continued challenge and if so what can be done to improve the environment?

• What do you see as the regulatory impact of these efforts and/or areas of future focus; "harmonization of efforts"
Have we done enough to empower/include/enthuse the public/patients/caregivers and if not how might we?

• Data sharing and joint-working seems to be working really well with clinical studies and human-data. How about preclinical and animal studies?