Industry Perspective World-Wide ADNI
North American-ADNI Private Partner Scientific Board (PPSB)

World-Wide ADNI Meeting
Vancouver, Canada, July 13, 2012

Johan Luthman, PPSB Chair 2012 (Merck & Co Employee)
Benefits of ADNI PPSB Partnership

Membership in the ADNI PPSB provides partners with opportunities to:

- Participate in an independent, pre-competitive forum for study-related scientific exchange among partners
- Participate in open ADNI Core discussions
  - Biomarkers, Biostatistics, Clinical, Genetics, MRI, Neuropathology, PET and Publications
- Engage and contribute to Biomarker progression via dedicated PPSB Working Group efforts
- Interact with ADNI PI/Core Leaders, colleagues from Pharma & Diagnostics companies, NIH and Regulators
- Network to other AD initiatives/organizations, such as Alzheimer’s Association, Critical Path Institute (CAMD)
- Opportunities to engage in WW-ADNI network
Impact of PPSB

- Partnership structure is the “gold standard” for an effective public-private partnership.

- Captive audience & provide input to other initiatives
  - For example National Alzheimer’s Project Act sponsored fora (e.g., Alzheimer’s Disease Research Summit 2012)
Current PPSB Partners in NA-ADNI

- Private partners committed more than $45 million to AD research through NA-ADNI (ADNI1 and ADNI2)
- Major contributions from industry also to J-ADNI, Pharma-Cog, etc.

- However, challenges for industry to participate across WW-ADNI initiatives
Industrial Aspect on WW-ADNI

**Key Deliverables from ADNI to Rx & Dx Industry:**

**Redefinition of Disease Stages**
- Identification of pre-dementia AD in MCI populations
- Feasibility Prodromal AD trials (pivotal drug trials)

**New Diagnostics & Prognostic Tools**
- Biomarker discovery & feasibility
- Biomarker supported diagnosis (diagnostic markers)
- Biomarker supported trial read-out (prognostic markers)
Redefinition of Disease Stages

Preclinical AD
Pre-Symptomatic
(Normal/pre-MCI)

Prodromal AD
Pre-Dementia
(Mild Cognitive Impairment)

Mild/moderate/severe AD
Dementia
(CURRENT Dx and Rx)

Subjects with risk factors; family history, dominant mutations or ApoE4 genotype

Early intervention may stop disease to occur

Pre-dementia form of AD identified by mild cognitive complaints and positive biomarker profiles

Early intervention may stop progression to AD diagnosis

Current AD diagnosis based on clinical symptoms; dementia of the Alzheimer’s disease type

Symptomatic treatment with AChEI or memantine

Primary/secondary prevention

Prevention of dementia

Treatment of Dementia

ADNI
Redefinition of Disease Stages

**Prodromal AD**
  - Late – MCI, Early - MCI
- World Wide “ADNI” efforts: PharmaCog (IMI/EU), AIBL (Australia), Japan-ADNI, etc.

- **Major impact on biomarker supported diagnosis of AD and definition Prodromal AD**

**Pre-symptomatic AD**
- Alzheimer’s Prevention Initiative (API)
  - PSEN1 carriers (Colombia) + APOE4 carrier populations (US)
- Dominantly Inherited Alzheimer’s Network (DIAN)
  - Preventative trials in autosomal dominant subjects (USA + EU)
- US Department of Defense – TBI veterans
- Several other initiatives on biomarker changes in Pre-symptomatic AD

- **Critical need to move further “upstream” in disease process to build feasibility for prevention trials**
Strategic Intent with AD biomarkers

Early Development—biomarker for **target engagement & proof of principle**
“Fit for purpose” biomarker in Phase I and II clinical trials

Late Development – Prognostic Biomarkers to **support drug label claims**
Treatment outcome measure (prognostic) in pivotal trials
Support of efficacy claims on disease modification effects

“Independent” Stand alone Diagnostic (vMRI, PET Imaging, IVD etc.)
Not associated with specific drug

Companion Diagnostic - Pharmacodiagnostic (IVD with Drug)
Post-drug development – Developed after drug launch; label update
Pre-drug development – Already commercialized test used in drug trial
Co-development—“True” CoDx with co-approval of Rx and Dx
### Application & Maturity of AD Biomarkers

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Companion Diagnostic Pathway

Pharmaceutical Drug

Drug Discovery  Preclinical  Clinical phases  Regulatory filing  Launch
Phase I  Phase II  Phase III

Biochemical Biomarker

Biomarker Discovery  Feasibility  Verification  IUO assay  Clinical Qualification  Regulatory review  Commercialization
RUO assay  Prototype  IVC

ADNI Effort
- Individual Dx/Rx companies
- Other Private-Public Partnerships
Efforts of Recently Formed PPSB-Initiated Working Group

- **Biofluid Biomarkers Working Group**
  - Collaborating on efforts to identify blood-based and CSF biomarkers for prodromal AD phase III trials – Forum for Dx and Rx companies to meet in general technical and scientific discussions
  - Supplementary effort to the Alzheimer’s Association Global Biomarkers Standardization Consortium’s Initiatives, CAMD, etc.

### Standardization of CSF biomarker assays

- Global Consortium for the Standardization of Biomarkers (Alz. Assoc.)
  - Reference Material & Methods effort for CSF Biomarkers
  - Collection, storage and sample processing
- ADNI - PPSB: Biomarkers Working Group
  - Align efforts on CSF IVD between Pharma and Diagnostics Companies

### Regulatory interactions biomarker qualification

- Critical Path Institute/CAMD:
  - Qualification opinions requests: vMRI (EMA & FDA), CSF BMx (FDA) etc.
- Individual Pharmaceutical or Diagnostic companies:
  - Qualification opinions requests: CSF BMx (EMA) and Amyloid PET (EMA)
Past Efforts
PPSB Working Groups/ fNIH Consortium

- Plasma Proteomics project
  - fNIH Biomarkers Consortium (special support Pfizer)
  - ADNI-I plasma samples - RMB analyses; Data delivered 2010

- A Beta as a Biomarker Working Group
  - CSF Placebo “drift” precompetitive study (PPSB only)
  - Healthy volunteer placebo phase I studies with continuous CSF sampling (and monkey data)
  - Analyze possible causes of the “drift” issue

**Biological reason?**
- CSF flow effect
- Subject dependent
- Leakage differences

**Technical reason?**
- Stickiness to the catheter
- Aggregation of the peptide
Ongoing Efforts via fNIH Consortium

- CSF Targeted Proteomics Project
  - fNIH Biomarkers Consortium
  - ADNI-I CSF samples
  - RMB analyses
  - Abstracts/posters at AAIC meeting in Vancouver

- BACE1 activity (and sAPPbeta)
  - Merck sub-study
  - Data submitted to ADNI April, 2012
Current Efforts of Established PPSB-Initiated Working Groups

- Informatics Working Group (formerly Database Working Group)
  - Working with Core Leader(s) to improve ADNI data interrogation systems

- PET Imaging Endpoints Working Group
  - Collaborating with existing initiatives to identify early AD imaging biomarkers and standardize Amyloid PET tracers

- Neuropsychology & ADAS-Cog PLUS Working Groups
  - Identify and/or develop clinical rating instrument for prodromal AD based on ADAS-Cog data set from ADNI-I
  - Supported by subgroup of NA-ADNI PPSB companies
New Initiative
PPSB-Initiated Working Group

- Clinical End Points Working Group

- To provide a forum for dedicated research and analyses by PPSB members to further unlock the potential of ADNI cognitive and functional data for future clinical trial design
  - An improved understanding of cognitive and functional trajectories in specific populations on existing endpoints
  - A critical appraisal of methodologies and development of an acceptable “toolbox” for endpoint optimization and novel endpoint development
  - New endpoints derived from data on existing measures with improved performance in specific populations
Data from global sites provide biochemical biomarker (CSF and plasma), MRI, and PET data on various populations (ethnic etc.) for use in planning phase III trials

- Highlight global standardization challenges (e.g. CSF measures differences)

Understanding the global technical and logistical challenges with biomarker supported patient recruitment

- Differences in SoC, use of biomarkers, infra-structure

Opportunities to learn from different regulatory agencies (e.g. FDA, EMA, PMDA, etc.)
2012: An Exciting Year for Alzheimer’s Disease

- Proof of Concept for anti-Aβ monoclonal antibodies (Aβ clearance principle)
- β-secretase inhibition moves into patients (Aβ reduction principle)
- Gamma-secretase inhibition further clarified
- Regulatory approval of an Amyloid PET ligand
- Critical progression of AD biomarker qualification efforts
- Initiatives of National Alzheimer’s Project Act

And much more this year…………….
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