Anti-amyloid treatment in Asymptomatic* AD A4 Trial

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Clinical Trial Site Investigator:

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Alzheimer’s Association
American Federation of Aging Research
American Health Assistance Foundation
A4 Trial Rationale

- Multiple trial failures at the stage of mild to moderate dementia with anti-Aβ therapies, despite evidence of biological activity.
- Converging data from both genetic at-risk and age at-risk cohorts suggest that the pathophysiological process of AD begins > decade prior to dementia.
- Need to actually test the amyloid hypothesis at a stage of AD when Aβ may drive the cascade and before widespread irreversible neuronal damage.
- The therapeutic success of the study does not require that Aβ is the cause of AD, merely that it is a critical early factor in the pathogenesis of AD.
Testing the Right Target and Right Drug at the Right Stage of AD

Aβ accumulation

Cognitive impairment

Abnormal

Normal

No pathology

Preclinical

MCI

Dementia

Clinical disease stage

Primary Prevention
Delay onset of AD pathology
- Decrease Aβ_{42} production
- Prevent tangle formation

Secondary prevention
Delay onset of cognitive impairment in individuals with evidence of pathology
- Decrease accumulated Aβ burden
- Decrease neurodegeneration with anti-tau or neuroprotective agents

Tertiary prevention and treatment
Delay onset or progression of dementia
- Neuroprotection-prevent neuronal loss
- Enhance function of remaining neurons
- Neurotransmitter repletion

Sperling, Jack, Aisen Science Trans Med 2011
A4 Trial Synopsis

- Secondary prevention trial in clinically normal older individuals (> age 70) Aβ+ on PET imaging
- Treat with biologically active compound for 3 years randomized, double-blind, placebo-controlled trial
  - Total N=1000 (N=500 per treatment arm)
  - At least 2 year additional clinical follow-up
- Include Aβ- arm (N = 500) for natural history study
- Ethics substudy: Disclosure of Aβ (J. Karlawish)
- Novel outcome development substudies: computerized cognitive test battery and task-free functional connectivity MRI
A4 Rationale: Older Aβ+

- More than 1/3 of clinically “normal” individuals over age 65 harbor amyloid plaque pathology
- Clinically normal older individuals with biomarker evidence of Aβ accumulation demonstrate functional and structural neuroimaging abnormalities, subtle cognitive deficits, and increased likelihood of cognitive decline similar to MCI and AD dementia
- Unlike autosomal dominant AD, there is a nearly unlimited pool of potential older subjects, but much less certainty about progression to dementia
Harvard Aging Brain Study
PiB-PET Amyloid Imaging

Sperling R et al *NeuroMolecular Medicine* 2010
Amyloid Imaging
in Normal Older Cohorts

AIBL Study

Mayo Clinic

Wash U

Villemagne and Rowe

Kantarci and Jack

Mintun and Morris
Preclinical Alzheimer’s Disease?

Prevalence of PiB+ve PET in HC

Prevalence of plaques in HC

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

~15 yrs

Prevalence of AD
(Tobias, 2008)

Rowe C et al Neurobiology of Aging 2010
Aβ burden in normal elderly associated with default network dysfunction in task and task-free fMRI

Sperling et al. *Neuron* 2009
(Also see Vannini *Neurobio of Aging* 2011; Vannini *Cerebral Cortex* 2012; Kennedy *NeuroImage* 2012)

Hedden et al. *J Neurosci* 2009
(Also see Sheline *Bio Psych* 2010; Mormino *Cerebral Cortex* 2011; Drzezga *Brain* 2011)
Aβ-associated reduction in cortical thickness in clinically normal elderly

(Also Schott *Annals* 2010; Dickerson *Cerebral Cortex* 2009; *Neurology* 2011; Sabuncu *Arch Neurology* 2011; Chetalat *Neurology* 2012)
The continuum of Alzheimer’s disease

Cognitive function

Asymptomatic

Early symptomatic

Preclinical

“Normal” Aging

MCI

Dementia

Years

Sperling R et al Alz & Dementia 2011
$^{18}$F-AV-45 Representative Images: Healthy Controls

Amyloid Negative HC

Amyloid Positive HC
Cognition in Aβ Pos vs. Neg in HC > 70 years old

Florbetapir (^{18}F AV-45) Phase II Study

Sperling R et al Neurobiology of Aging 2012
Superman in his later years
Amyloid associated memory performance impairment in “normals”

Interaction with Cognitive Reserve

Rentz D et al *Ann Neurol* 2010
(also see Roe et al 2010, 2011)

Face-name associative memory exam

Rentz D *Neuropsychologia* 2011
(also see Amariglio R et al. *J Clin Exp Neuropsychol* 2012)
Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

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Staging Framework for Preclinical AD

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ₁₋₄₂

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI ➔ AD dementia

Sperling R et al Alzheimer’s & Dementia 2011
Hypothetical model of AD pathophysiological cascade

- **Age**
- **Genetics**
- **Cerebrovascular risk factors**
- **Other age-related brain diseases**
- **Amyloid-β Accumulation**
- **Synaptic Dysfunction**
- **Glial Activation**
- **Tangle Formation**
- **Neuronal Death**
- **Brain and cognitive reserve**
- **Environmental factors**
- **Cognitive Decline**

Sperling et al *Alzheimer & Dementia* 2011
NIA-AA Preclinical Workgroup
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- Environmental factors

Sperling et al. Alzheimer & Dementia 2011
NIA-AA Preclinical Workgroup
A4 Specific Aims

• To determine whether treatment with an anti-amyloid agent will slow the rate of cognitive decline in clinically normal older Aβ+ individuals at risk for progression to MCI and AD dementia

• To investigate the impact of anti-Aβ treatment on “downstream” markers of neurodegeneration, and explore whether there is a “critical window” for anti-Aβ therapy within the preclinical stages of AD

• To develop more sensitive outcome measures to improve the efficiency of future secondary prevention trials
A4 Trial Synopsis

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A4 Screening and Randomization

Figure XX: Schema of screening algorithm to achieve enrollment goals

- Telephone Screen \( N > 10,000 \)
- In clinic screen \( N = 5000 \)
- PET Amyloid imaging \( N = 3300 \)
- Obtain MRI on \( A\beta \) + MRI OK \( N = 1000 \)
- \( A\beta + \) MRI OK

<table>
<thead>
<tr>
<th>Natural History Arm of ( A\beta ) – (Age and education matched)</th>
<th>Placebo completers ( N = 375 )</th>
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<tbody>
<tr>
<td>Active Treatment ( N = 500 )</td>
<td>Treatment completers ( N = 350 )</td>
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Randomization (with stratification)
Subjects Inclusion Criteria

• Ages 70 – 85; Positive on PET amyloid imaging
• One out of five from under-represented minority
• MMSE 27-30 (Education adjustment)
• CDR 0 – Will allow subtle subjective memory complaint if no evidence of impaired function
• Logical Memory II score of 15 – 9 for high education

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<td>Mean (sd) of normative group</td>
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<td>13.7 (4.2)</td>
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A4 Clinical Outcome Measures

• Primary outcome – Rate of decline on Cognitive Composite
  – Episodic memory – Free and Cued Selective Reminding delayed recall and LM paragraph recall
  – Timed executive function test – Digit Symbol
  – MMSE

• Secondary clinical outcomes
  – Novel computerized battery – face-name memory, object pattern separation, attentional measures CogState
  – Patient reported outcomes – e-COG, others
  – CDR Sum of Boxes
A4 Biomarker outcomes

• PET amyloid imaging – decrease in mean cortical SUVr
• CSF phospho-tau and tau (in subset)
• Volumetric MRI
  – Cortical thinning
  – Hippocampal atrophy
• Functional MRI
  – Default network connectivity
• Consider FDG in subset if can obtain additional funding
Multi-center Task-free Functional Connectivity: DIAN

Chhatwal et al. AAIC 2012
A4 – Power Calculations

• Primary outcome – Cognitive Composite
• Utilized longitudinal data sets from ADCS, AIBL, ADNI, Wash U comparing Aβ+ vs. Aβ- decline
• Ran large number of analyses assuming:
  – Power=.80 to detect 30% difference in rate of decline
  – 30% attrition, MMRM model, alpha 0.05 two-sided
• Total N =1000 (500 per treatment arm) yields power to detect 28-32% difference in rate of cognitive decline over 3 years
• Well-powered to detect change on biomarkers
Natural History Arm

- Will screen fail 60-70% of A4 subjects for randomization to treatment arms
- Important group to capture baseline cognitive measures and blood samples – gold standard Aβ–
- Plan to follow at least 500 Aβ– matched for age, education in natural history arm. Current plan is clinical and cognitive assessments only
- Work to find funding to obtain biomarkers and follow-up imaging, potentially enlarge sample and study as natural history aging cohort
A4 Ethical Considerations

• Will be revealing amyloid status to normal subjects
• Unknown risk at individual subject level of progression to MCI and AD dementia
• Risks of biologically active anti-amyloid agents
• A4 Ethics substudy
  – Pilot work on language for consent form and factors that impact likelihood of participation
  – Substudy project within A4 to assess impact of consent process and of revealing amyloid status to both amyloid positive and negative individuals
A4 Decisions–Therapeutic Agent

- Must have evidence of biological activity/target engagement and adequate safety data to support a 3 year trial in clinically normal older subjects
- Company willing to partner with ADCS
- Considering combination trials (2 x 2 factorial)
- Process for selection: partnership with DIAN treatment selection committee, final approval by the ADCS steering committee
- Current plan for decision late 2012/early 2013
Collaboration for Alzheimer’s Prevention

- A4, API, DIAN, other international prevention efforts, Alzheimer’s Association, NIA
- Harmonize the primary outcome measures
  - If not identical then at least overlapping tests
  - Cross validation computerized cognitive composite
- Harmonize biomarker and imaging data acquisition for comparability
- Joint meetings with regulatory authorities
- Working together on selection of therapeutic agents
Urgency

• We are running trials at the end stages of a disease process that begins decade(s) before dementia
• Think about what happens when we wait to treat until after symptoms are clearly evident in cancer, HIV, stroke, osteoporosis, cardiac disease, diabetes... and the success with preventative Tx
• We have 20,000 baby-boomers turning age 65 every day in the US entering the age of risk
• We have many challenges but we must make the best decisions possible based on currently available data and move forward
Acknowledgments

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