Long-term Treatment Trials in Alzheimer's Disease: Ongoing Trials

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Summary of Ongoing Studies Using Amyloid Modifying Therapies for AD – Part 1

Sponsor	Drug	Design	Population	Key Measures	Status
Prodromal AD					
BMS	BMS-708163 (γ-secretase inhibitor)	Ph.2, MC, randomized, DB, PBO-controlled study to evaluate safety, tolerability and PK/PD	Prodromal AD; 45-90 yrs; MMSE 24-30 CSFAβ42 <200pg/ml Ttau/Aβ ≥ 0.39	**1°**: Safety/tolerability **2°**: CSF biomarkers (Aβ40, Aβ42, Ttau, Ptau) progression to dementia	Active, not recruiting
Roche	Gantenerumab (humanized Aβ antibody)	Ph.2, randomized, DB, PBO-controlled study to evaluate effects on cognition, functioning, safety and PK; 104 weeks	Prodromal AD; 50-85 yrs.; MMSE ≥24; <u>not</u> receiving AChEIs or Memantine	**1°**: CDR-SB, **2°**: ADAS-Cog, FAQ, safety, PK	Recruiting
Mild / Moderate AD					
Genentech	MABT5102A (humanized Aβ antibody)	Ph.2, randomized, PBO-controlled study to evaluate effects on brain amyloid burden	Mild/mod. AD; MMSE 18-26; 50-80 yrs	**1°**: PET (amyloid) **2°**: CSF biomarkers, FDG-PET, ADAS-Cog	Recruiting
Lilly	LY2062430 (solaneuzumab) (humanized Aβ antibody)	Ph.3, 19-mo., randomized, PBO-controlled study to evaluate effects on AD progression; + EXPEDITION EXT (OL, extension)	Mild/mod. AD; >55 yrs	**1°**: ADAS-Cog, ADCS-ADL **2°**: CDR-SB, NPI, vMRI, RUD, QOL, plasma Aβ	Active, recruiting in EXT study
		Ph.2, single infusion, effects on plasma Aβ	<u>4 groups</u>: Mild DAT, possible AD, elderly (no AD), young	**1°**: plasma Aβ – frag. 2 **2°**: plasma Aβ1-40, 1-42, other fragments	Recruiting

Information obtained from ClinicalTrials.gov on 15 February 2012

Summary of Ongoing Studies Using Amyloid Modifying Therapies for AD – Part 2

Sponsor	Drug	Design	Population	Key Measures	Status
Mild / Moderate AD (continued)					
Pfizer	PF-04360365 (ponezumab) (humanized Aβ antibody)	Ph.1, randomized, Investigator/pt. blinded, PBO-controlled study to evaluate clearance of Aβ from CSF, PK, safety & tolerability	AD patients, healthy volunteers	Aβ clearance in 24 hrs.	Recruiting
Pfizer	Bapineuzumab (humanized Aβ antibody)	2 Ph. 3 studies: randomized, PBO-controlled, efficacy/safety; 1.5 yrs.; one in APOE4 non-carriers, one in APOE4 carriers	Mild/mod. AD; 50-88 yrs; MMSE 16-26; brain MRI	**1°**: ADAS-Cog, DAD **2°**: Brain amyloid (PET), CSF Ptau, vMRI, time to progression, CDR-SB,	Recruiting
Pfizer/ Janssen	ACC-001 + QS21 (active immunization)	Ph.2a, 24-mo., MC, randomized, 3rd party unblinded, adjuvant and PBO-controlled, MAD study to evaluate safety, tolerability and immunogenicity	Mild/mod. AD; 50-85 yrs; MMSE 16-26	**1°**: TEAEs, other safety **2°**: Immunogenicity, blood levels of anti-Aβ IgG and IgM	Recruiting

Information obtained from ClinicalTrials.gov on 15 February 2012

Summary of Current Studies in Prodromal AD – Part 1

Study	Design/Objective/Population	Location	Key Measures	Timeline	Funding
ADNI	5-yr. trial to define rate of progression from MCI to AD to improve design of clinical trials. Subjects: 200 Elderly Controls, 400 MCI, 200 AD	57 centers in US and Canada	MRI scans, PET scans, biomarkers in CSF & blood, cognitive tests	Start 2004; end 2010; ADNI GO continuing; 180 papers published	NIH, Pharma, Alz. Assoc., other
AIBL	Prospective, LT study of ageing to assess disease progression, develop and confirm diagnostic markers/biomarkers and psychometrics, and asses effect of lifestyle. Subjects: 211 AD, 133 MCI, 768 healthy volunteers	Australia	Cognitive tests, health and lifestyle questionnaire, blood markers, PIB-PET, MRI, ActiGraph	Start 2006; 18-mo. follow-up done	Australian gov't
DIAN	Int'l research partnership to understand rare form of AD caused by genetic mutation; enroll subjects with parent who had mutation	11 centers in US, UK, Australia	Neuropsych. testing, blood & CSF markers, brain imaging (MRI, FDG and PIB PET), genetic testing	Currently enrolling	Multi-yr. grant from NIA
	Treatment study; carriers assigned to drug or placebo (3:1) in first phase, 80 patients/group;	US, UK, Australia	Phase 1: imaging of amyloid, cognition, other biomarkers Phase 2: Cognitive test battery, biomarkers	Initial 2-year study, followed by long-term 3-year trial	NIA?, Pharma to provide drugs

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing; DIAN, Dominantly Inherited Alzheimer's Network

Summary of Current Studies in Prodromal AD – Part 2

Study	Design/Objective/Population	Location	Key Measures	Timeline	Funding
A4	Secondary prevention trial: treat older individuals at risk for AD (based on amyloid imaging biomarkers) with anti-amyloid therapy (TBD) to delay cognitive decline; subjects with pre-MCI (memory impairment); drug vs. placebo: 300-500 subjects per arm; 3-yr. treatment with long-term follow-up;	US and collaborate with AIBL & B.Vellas (FR)	PET (amyloid); cognition (working on battery)	Propose as part of ADCS-NIA grant in March 2012; expected start early 2013	NIA; anti-amyloid drug to come from Pharma
ICTUS (B.Vellas)	Prospective, 2-yr. observational study to determine if AChEIs change pattern of institutional-ization in European AD patients	37 EADC centers	**1°**: CDR change; **2°**: cognition, ADL, behavior, cost & caregiver burden; predictors of decline and response to AChEIs	Ongoing	EADC

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease; EADC, European Alzheimer's Disease Consortium; ICTUS, Impact of Cholinergic Treatment Use

Results of Clinical Trials with Amyloid Modifying Treatments that Have Failed to Demonstrate Therapeutic Effect

- No significant clinical benefit compared to placebo
  - AN1792 (interrupted for toxicity)
  - Alzhemed
  - R-flurbiprofen (Flurizan)
  - Bapineuzumab (Ph. 2)
  - BMS-708193 (Ph. 2; high incidence of d/c and rash at higher doses)
- Significant worsening (cognition, ADLs) compared to placebo
  - LY-450139
  - R-flurbiprofen (Flurizan)
- Potential reasons for failure of amyloid modifying compounds in trials to date
  - Poor brain penetration in man
  - No in-vivo effects on amyloid metabolism or clearance in man
  - Too short a period of treatment
  - Outcome measures insensitive to change
  - Inappropriate patient selection
  - **Or, is the target unlikely to benefit clinical symptoms in patients ?**

Diagnosis of Population at Risk for Developing AD

- Depression and other behavioral symptoms precede cognitive deficits by 2-3 years
- Functional deficits without memory deficit
- MRI – entorhinal cortex and medial temporal lobe atrophy, cortical thinning
- Magnetic Resonance Spectroscopy
- MCI – can intervention before MCI develops prevent progression to MCI/AD

Proposal for the Conduct of Clinical Trials in Prodromal AD (1)

- Patient Population:
  - Include patients who do not have any of the following:
    - clinical symptoms
    - significant structural changes in the brain
    - high CSF tau
  - Patients should have memory complaints and be positive for amyloid on PET
  - No restrictions on concomitant therapy at baseline
  - Allow patients with new concomitant Illnesses or medications to continue in the study

Proposal for the Conduct of Clinical Trials in Prodromal AD (2)

- Study Design:
  - Sample Size: large, i.e. 300+ patients per group
  - Duration: studies should be carried out for up to 10 years
  - Primary Endpoint: ~30% ↓ in rate of cognitive decline on a composite measure; ~3 years will most likely be required to show a drug/placebo difference
  - Other Measures: behavior, functional deficits, pharmacoeconomics, neuroimaging

Proposal for the Conduct of Clinical Trials in Prodromal AD (3)

- Study Design (cont'd):
  - At end of 3 years, Pharma to break blind internally, analyze data, and submit to Regulators
  - Patients will continue on blinded treatment during LT follow-up phase; alternative funding required
  - Adaptive design: If benefit demonstrated at 3 yrs., adjustment will be made to treatment groups
  - Centers to follow patients until ~30% have reached severe/very severe AD stage (i.e., GDS 6-7)
  - Data will be made available to all centers

Proposal for the Conduct of Clinical Trials in Prodromal AD (4)

- Regulatory/statistical issues that will need to be addressed:
  - Full stratification for all concomitant treatments and conditions will not be possible
  - Treatment will be added on to other drugs being taken at baseline, plus additional medication may be added at any time during the trial; how should the data be analyzed?

Design of Long-term AD Trials (1)

- Prior disease progression trials in AD were not successful because multiple pathological processes, e.g. tau and amyloid, not targeted
- Design: randomized, placebo-controlled trials, but allow patients who fail on assigned treatment to be switched to alternative therapy
- Cognition: use memory training, in addition to pharmacotherapy to prevent memory decline; need sensitive cognitive assessments
- Other symptoms: treat any symptoms and concomitant diseases as they occur

Design of Long-term AD Trials(2)

- Treatments:
  - New AD treatments, e.g. secretase inhibitors, immunoglobulins, omega-3 fatty acids, etc., should be added to approved therapies, i.e. Cholinesterase inhibitors, Memantine
  - Treat behavioral symptoms
  - Treat all concomitant illnesses, rather than discontinuing patients from the trial

Backup Slides

Design of Long-term AD Trials(3)

- Assessment of Efficacy:
  - Monitor outcome of treatment for behavioral symptoms
  - Look at effects on function/disability, in addition to cognition
  - Evaluate impact of treatment of concomitant depression, anxiety, etc. on long-term outcome
  - Adjust analysis for concomitant illnesses and treatments

Design Considerations for Long-term AD Trials (4)

- Pharmacoeconomic Considerations:
  - Will early intervention and long-term treatment reduce cost of care (caregivers, institutions)
  - Evaluate effects of education (patients/caregivers) and more aggressive treatment
  - Similar types of patients should be grouped for analysis, e.g. based on symptoms, concomitant diseases/medications, genetic markers, etc.

Long-term Trials for AD: Policy Issues (1)

- Need to initiate process for early identification of patients at risk for AD:
  - Neuroimaging – MRI, MRS, PET (learn from ADNI)
  - Genetic markers – APOE, APP, presenilin, other?
  - Biomarkers – tau, P-tau, Aβ1-42, other?
  - Identification of earliest markers of cognitive dysfunction and behavioral symptoms; determine relationship to objective measures of change in the brain, e.g. entorhinal cortex

Long-term Trials for AD: Policy Issues (2)

- Long-term follow-up: Continue to follow all patients and look for correlation between functional measures and brain imaging measures
- Examine effects of specific interventions on different populations defined by genetic markers, symptoms, etc.
- Continue to follow patients from 6-month studies in long-term treatment without placebo control; look at effect sizes, rather than statistically significant differences between drug and placebo
- Identify factors that influence disease progression