

# *Alzheimer's Disease: Moving Forward or Spinning our Wheels?*

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Vice President  
Defined Health





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<http://www.therapeuticinsight.com>

<http://www.ebdgroup.com/bpa/>

# Panelists



- **Moderator:** Ginger S. Johnson, VP, Defined Health
- Dale Schenk, PhD, Chief Scientific Officer, Elan
- Andrea Cavalli, Drug Discovery and Development, Italian Institute of Technology
- Sarah Holland, Global Head, CNS Partnering, Roche
- Manuel Lopez-Figueroa, VP, Bay City Capital

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*The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.*

# The Alzheimer's Crisis

**In the next two years, the first baby boomers will reach their 65th birthday. By 2029, all baby boomers will be at least 65 years old.**

An estimated 5,300,000 Americans have Alzheimer's disease and 1 in 10 individuals has a family member with the disease. By 2050, the number of individuals with the disease could reach 16,000,000 unless science finds a way to prevent or cure the disease.

# The Economic Burden of AD

The Dartmouth Center for Health Policy Research has calculated that Medicare beneficiaries with Alzheimer's cost three times more than beneficiaries without dementia.

**Average Per Person Payments by Source for Healthcare and Long-term Care Services, Medicare Beneficiaries Aged 65 and Older, with and without Alzheimer's Disease and Other Dementias, 2004**

Average Per Person Payments	Beneficiaries with no Alzheimer's or Other Dementia	Beneficiaries with Alzheimer's or Other Dementia
<b>Total payments*</b>	<b>\$10,603</b>	<b>\$33,007</b>
Medicare	5,272	15,145
Medicaid	718	6,605
Private insurance	1,466	1,847
Other sources	211	519
HMO	704	410
Out-of-pocket	1,916	2,464
Uncompensated care	201	261

\* Payments by source do not equal total payments exactly due to the effect of population weighting.  
Created from data from Bynum, *Medicare Current Beneficiary Survey*.<sup>23</sup>

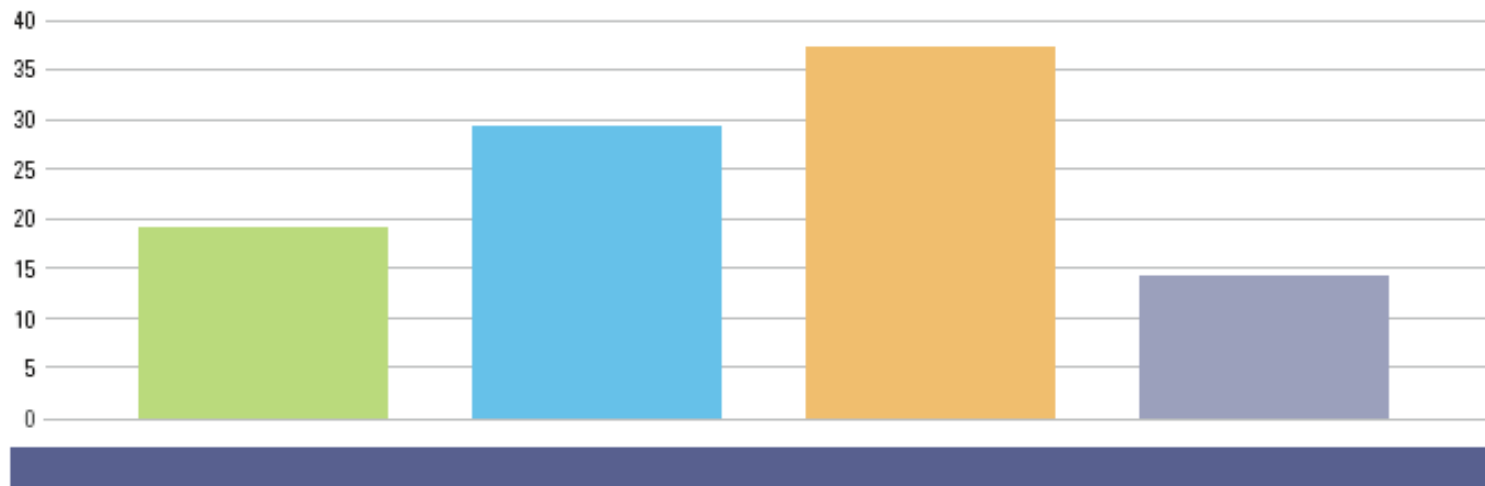
# Alzheimer's is Not Just a Disease of the Patient

Alzheimer's disease is a family disease. In 2009, 10 million caregivers will provide 94 billion hours of physically demanding and emotionally draining uncompensated care.

**Ages of Alzheimer and Other Dementia Caregivers, 2003**

Under 35 35-49 50-64 65+

Percent



Created from data from *Families Care: Alzheimer's Caregiving in the United States*.<sup>27</sup>

# A National Alzheimer's Strategic Plan

A National  
Alzheimer's Strategic Plan:  
THE REPORT OF THE ALZHEIMER'S STUDY GROUP

- The Alzheimer's Study Group, an independent panel co-chaired by former Speaker Newt Gingrich (R-Ga.) and former Sen. Bob Kerrey (D-Neb.), with other prestigious members including Supreme Court Justice Sandra Day O'Connor and Harold Varmus, recently found that those with Alzheimer's will cost taxpayers \$20 trillion in Medicare and Medicaid costs over the next 40 years.
- "If we correctly thought that one stimulus bill costing \$787 billion was mind-boggling, the study group's finding suggests that what we'll pay for Alzheimer's, if we don't find a way to stop it, will equal 25 stimulus bills over the next four decades."

Johns, H. Sept 21, 2009 Special to Roll Call <http://www.rollcall.com/news/38731-1.html>

# S. 1492: Alzheimer's Breakthrough Act of 2009

The Alzheimer's Breakthrough Act (S. 1492 and H.R. 3286), introduced by Sens. Barbara Mikulski (D-Md.) and Kit Bond (R-Mo.) and Reps. Ed Markey (D-Mass.) and Chris Smith (R-N.J.), would authorize \$2 billion in funding for Alzheimer's research and introduce other changes that would expedite the development pipeline.



Introduced



Referred to Committee



Reported by Committee



Senate Vote



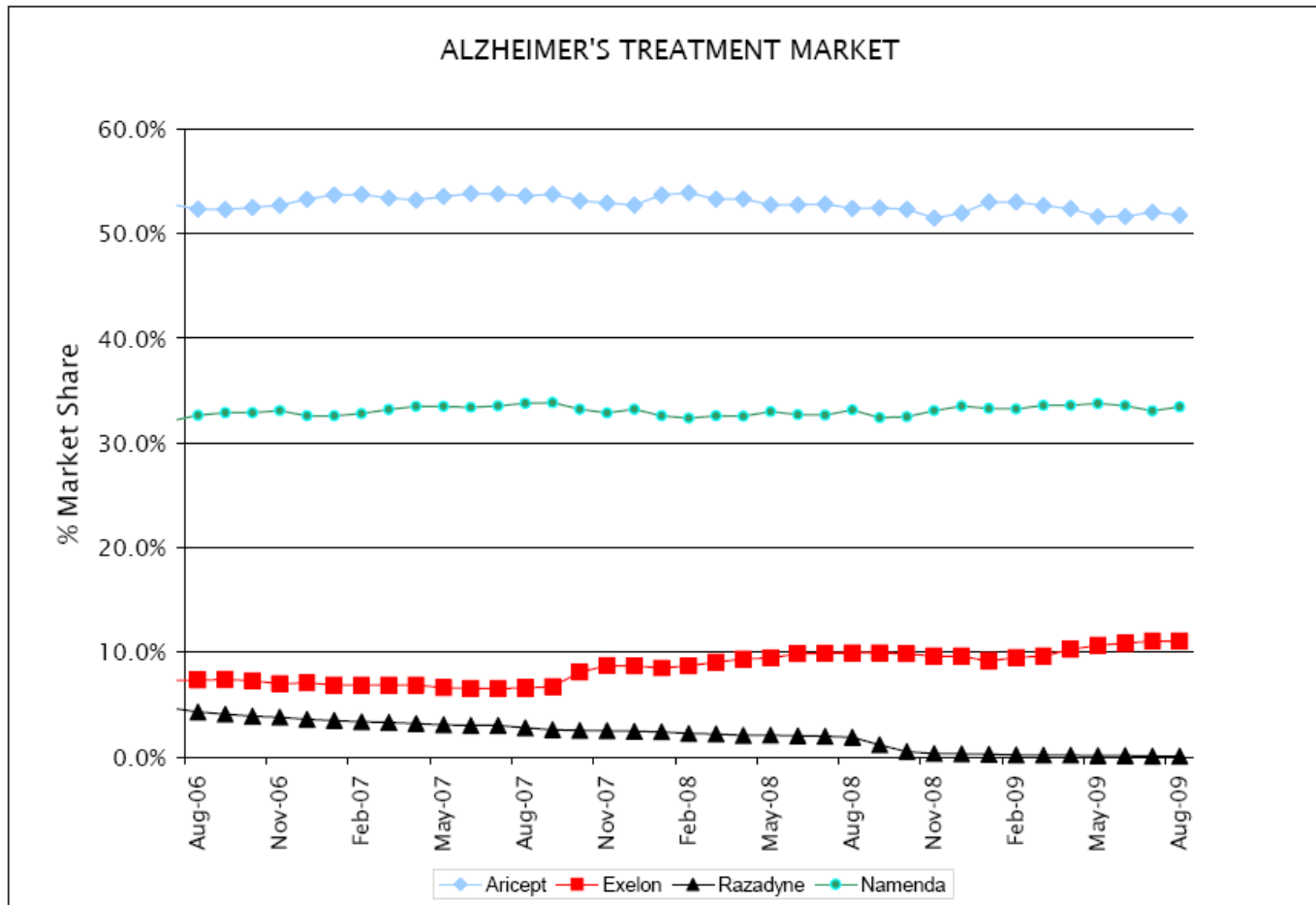
House Vote



Signed by President

# The Current State of Therapy for AD

Currently available AD treatments provide symptomatic relief, temporarily, but do not alter the underlying disease process. Even so, WW sales in 2008 exceeded \$3 billion.

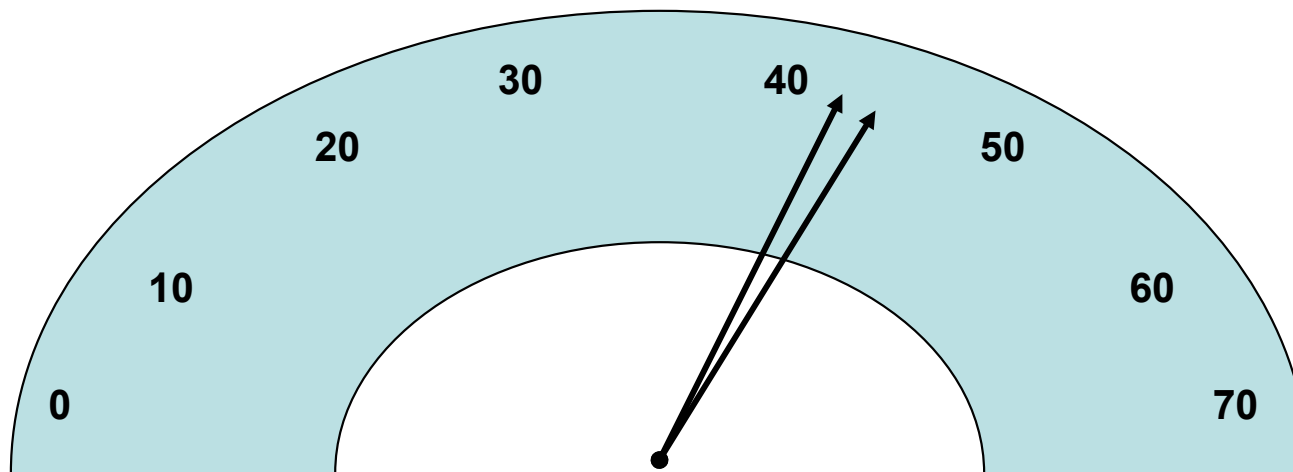


Source: IMS Monthly Rx audit

Cowen and Company Therapeutic Categories Outlook Sept. 2009

# Aricept: Tops in Revenue, but Barely Moves the Efficacy Needle

- In a 30 week pivotal Phase III for Aricept, 473 patients received 5mg or 10 mg. After 24 weeks, the change in ADAS-cog scores were 2.8 and 3.1 units respectively (70 point scale) which was significant compared to placebo, but relatively modest from a clinical perspective.
- Aricept sales are expected to be \$2B in 2009 in the US; loses patent protection in 2010.

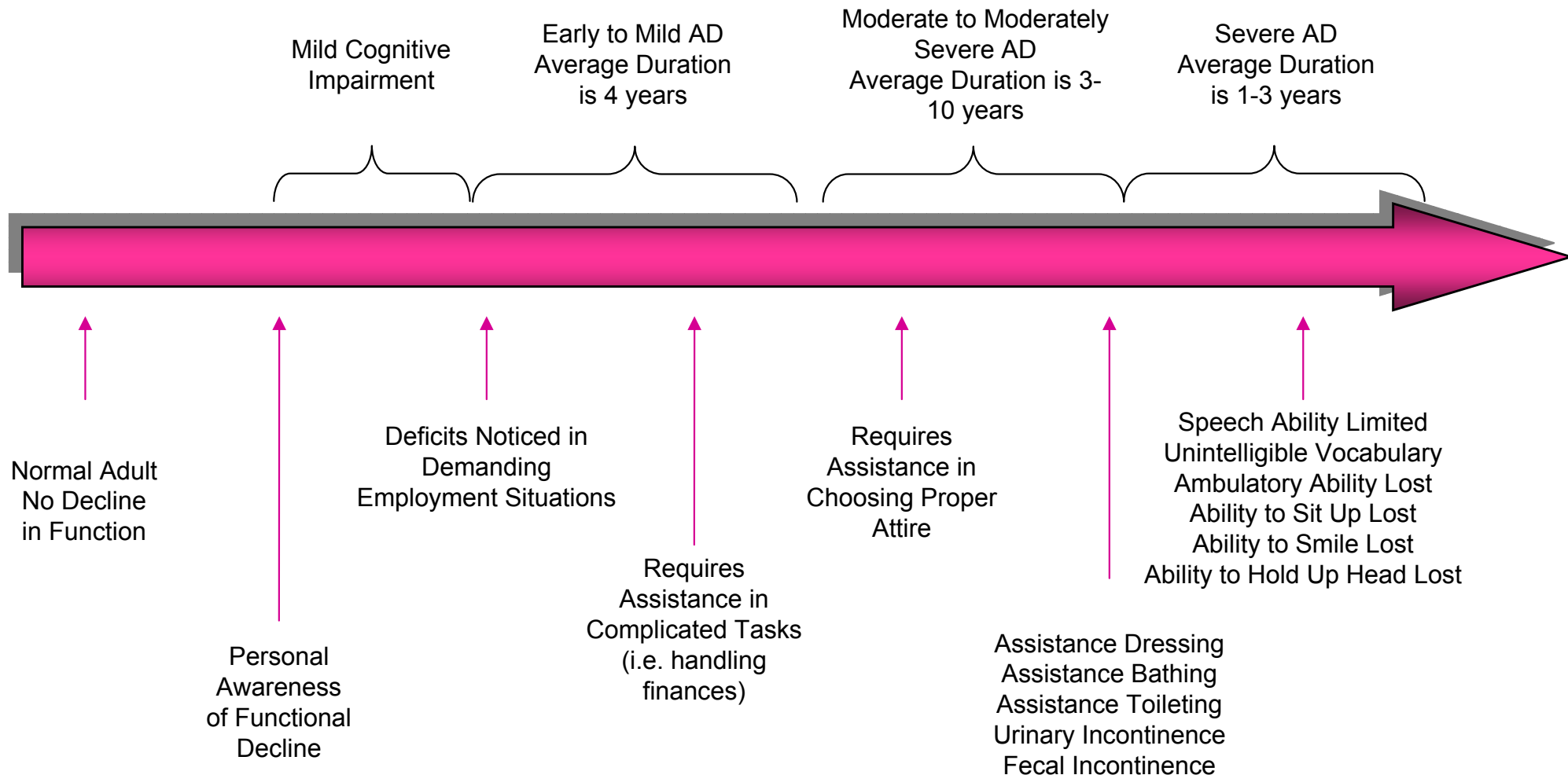


**ADAS-cog**

The average AD patients gains 6-12 ADAS-cog units in a year.

# The Benefit of Currently Available Symptomatic Therapy Does Not Outweigh the Cost (\$5-\$6/day) and Side Effects – at Least Not For Long

The average Alzheimer's patient is on symptomatic therapy for a year or less. While disease duration can be 20 years.



Source: Alzheimer's Association

# The Newest AD Therapy: Medical Food



## **1. Indications and Usage**

Axona (caprylidene) is a medical food (see Section 11 “Description” below) containing a proprietary formulation of medium-chain triglycerides (MCTs), specifically caprylic triglyceride, for the clinical dietary management of the metabolic processes associated with mild to moderate Alzheimer’s disease (AD). Axona is taken orally once a day, and must be administered under physician supervision and dispensed by prescription.

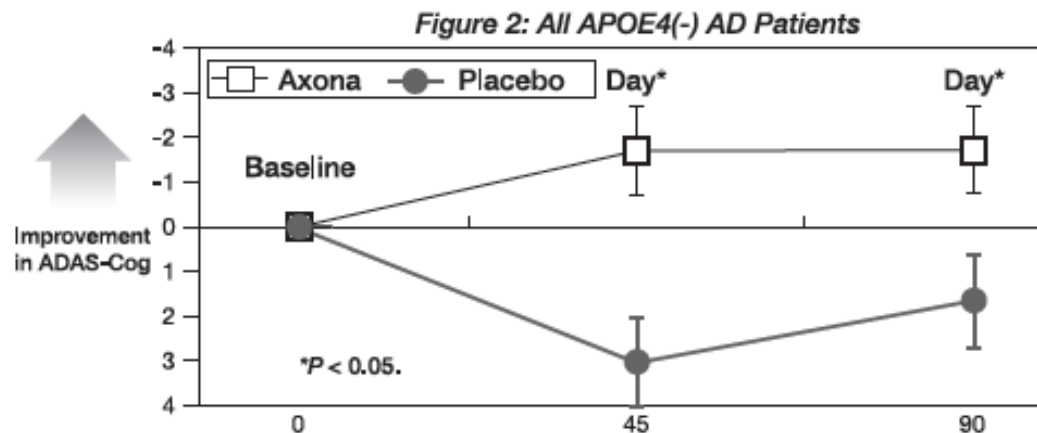
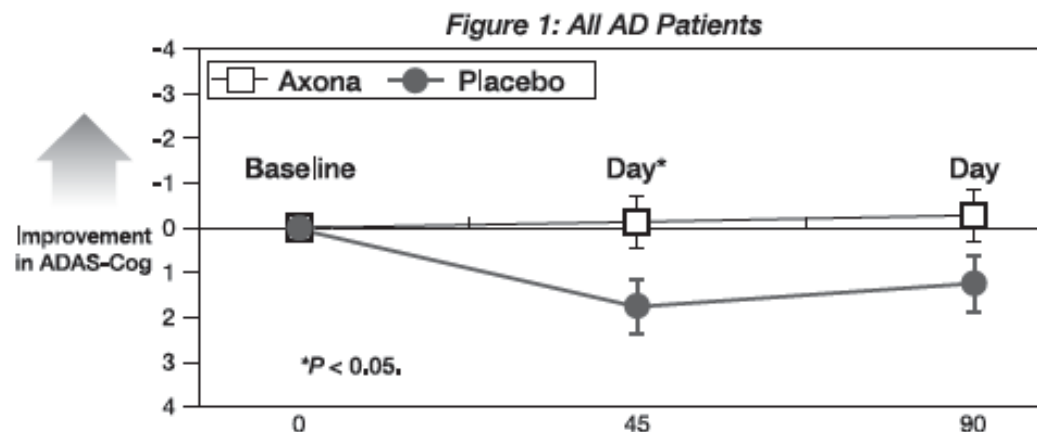
# Axona: Medical Food as a Strategy, Not a Fallback

Axona (Accera) has been tested in 3 clinical trials in populations of patients with a diagnosis of probable mild-to-moderate AD and MCI, as well as in healthy elderly volunteers. Axona is the first prescription product for the treatment of AD with label data showing how efficacy differs in a genetic subset of patients (ApoE4-).

Double-blind, randomized, placebo-controlled, 90-day study with a 2-week washout period performed at multiple US clinical centers in a population of 152 patients with mild to moderate AD, randomized 1:1 to receive placebo or Axona.

APOE4(-) patients showed greater improvement compared to APOE4(+) patients in the AD Assessment Scale—Cognitive subscale (ADAS-Cog, which measures memory and other aspects of cognitive performance) ( $P = 0.039$ ).

Double-Blind Alzheimer's Disease Clinical Study:  
Change in Mean Total ADAS-Cog Scores Over Time



# The Holy Grail: Disease Modification / Delay

Disease modification (DM) can be defined as treatments or interventions that **affect the underlying pathophysiology** of the disease and **have a beneficial outcome** on the course of Alzheimer's disease.

# BAPTists versus TAU(o)ists



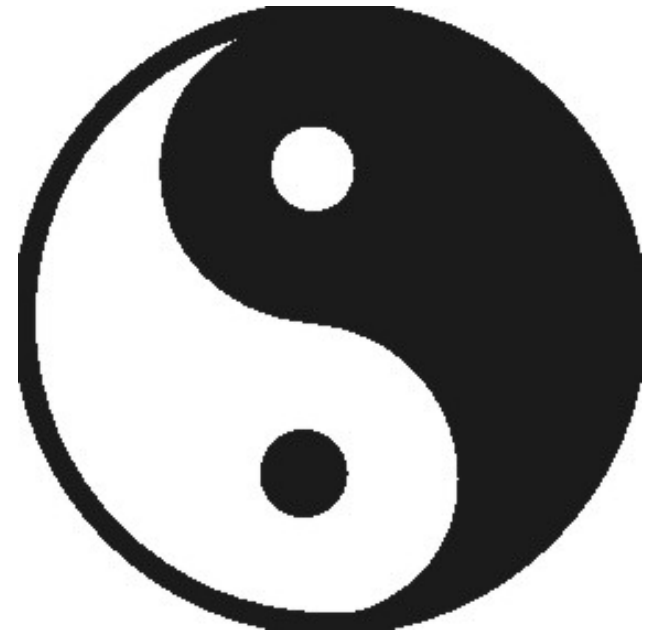
**Beta Amyloid Precursor Protein**



**Beta Amyloid**



**Amyloid Plaques**



**Tau**

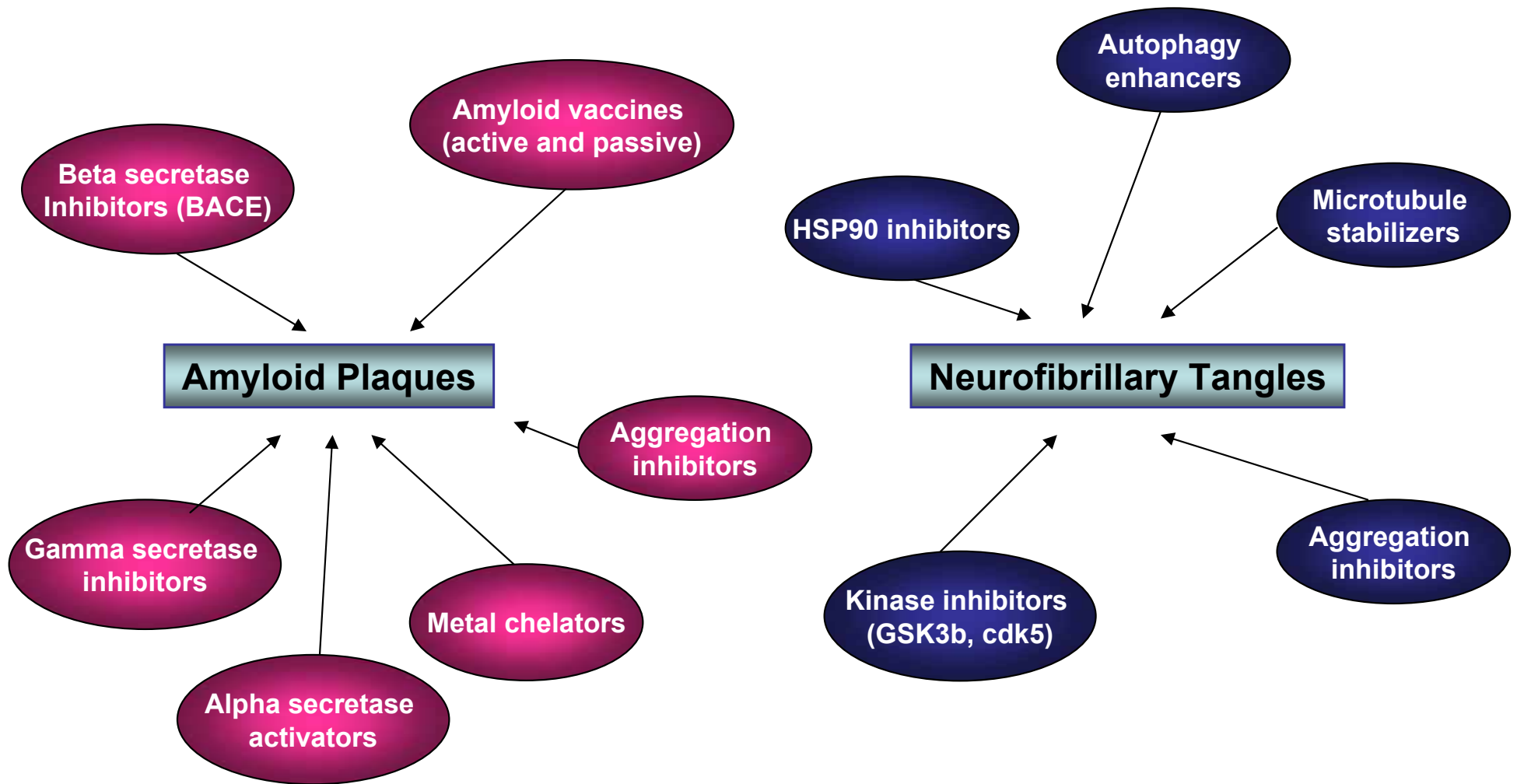


**Hyperphosphorylated Tau**



**Neurofibrillary Tangles**

# Multiple Points of Attack



# BAPtists Outnumber TAU(o)ists 3:1



- AC Immune/Genentech (A $\beta$  vaccine)
- Actelion (BACE)
- Acumen/Merck (ADDL)
- Affiris/GSK (A $\beta$  vaccine)
- Archer Pharmaceuticals (BACE, gamma secretase)
- Baxter (IVIg)
- Chiesi (gamma secretase/NSAID)
- CoMentis/Astellas (BACE)
- Eisai – from TorreyPines (gamma secretase)
- Elan/Wyeth/Pfizer/J&J (A $\beta$  vaccine)
- Elan (A $\beta$  vaccine, secretase inhibitors)
- EnVivo Pharmaceuticals (gamma secretase)
- Evotec (BACE)
- GSK (Ab vaccine)
- Intellect Neuroscience (A $\beta$  vaccine)
- Eli Lilly (gamma secretase, A $\beta$  vaccine)
- Merck (Ab vaccine, BACE)
- Noscira Therapeutics (A $\beta$  aggregation)
- Novartis/Cytos (A $\beta$  vaccine)
- Pfizer/Rinat (A $\beta$  vaccine)
- Pfizer (gamma secretase)
- Prana (metal chelator)
- Roche (A $\beta$  vaccine)
- Transition Therapeutics/Elan (A $\beta$  aggregation)
- Wyeth (BACE, gamma secretase)

- TauRx (tau aggregation)
- Abbott (GSK-3b inhibition)
- Lundbeck (GSK-3b inhibition)
- Noscira (GSK-3b inhibition)
- Pfizer (kinase inhibition)
- Oligomerix (tau aggregation)
- Allon Therapeutics (microtubule stabilization)
- Intellect Neuroscience (discovery)
- Eli Lilly/Applied NeuroSolutions (discovery)

Adis R&D Insight

# TAU(o)ists are Fighting Back



## Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies

*Kurt R. Brunden, John Q. Trojanowski and Virginia M.-Y. Lee*

Abstract | Neuronal inclusions comprised of the microtubule-associated protein tau are found in numerous neurodegenerative diseases, commonly known as tauopathies. In Alzheimer's disease — the most prevalent tauopathy — misfolded tau is probably a key pathological agent. The recent failure of amyloid- $\beta$ -targeted therapeutics in Phase III clinical trials suggests that it is timely and prudent to consider alternative drug discovery strategies for Alzheimer's disease. Here, we focus on strategies directed at reducing misfolded tau and compensating for the loss of normal tau.

**The recent failure of amyloid- $\beta$ -targeted therapeutics in Phase III clinical trials suggests that it is timely and prudent to consider alternative drug discovery strategies for Alzheimer's disease.**

# TauRx Puts Tau in the Headlines



## **Breakthrough drug 'could halt' Alzheimer's**

Wed July 30, 2008

Announced at Alzheimer's Association International Conference in Chicago

Rember™\* is first drug to act on the "tangles" discovered by Alois Alzheimer

Tangles destroy nerve cells and neurons critical for memory

If further trials prove successful, the drug could be available by 2012

*\*Rember is methylene blue, a phenothiazine compound that has been around for over 100 years as common laboratory dye and used to treat urinary tract infections and some hemoglobin disorders.*

# Phase II Shows 81% Reduction in Mental Decline

- TauRx tested Rember in patients with mild and moderate Alzheimer's disease in the UK and Singapore.
- Those taking a 60 mg dose of Rember experienced an 81 percent reduction in mental decline compared with the placebo group.
- The decline seen in patients treated with Rember was not significantly different from their starting score to the assessment at one year and at their final assessment at 19 months, while patients on placebo continued to decline.
- In addition to cognitive tests, patients had repeat brain scans at the start of the study and after 25 weeks. This showed that the treatment effect was greatest in the hippocampus, an area of the brain affected by Alzheimer's tang

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[http://www.timesonline.co.uk/tol/life\\_and\\_style/health/article4425218.ece](http://www.timesonline.co.uk/tol/life_and_style/health/article4425218.ece)

# And the Amyloid – Tau Debate is On

**The amyloid theory "is in a meltdown,"** says Claude Wischik of the University of Aberdeen, a founder of the biotech TauRx Therapeutics. He argues that the amount of amyloid in patient brains doesn't correlate much with dementia, and blocking tau, a second protein that accumulates in the brain cells of demented patients, as his company is doing is a much better way to go. **"I could never understand why people were so persuaded by the amyloid theory. It is more about sociology than science,"** he says.



But Pfizer neurologist Larry Altstiel counters the **amyloid theory "is alive and well. It is pretty hard to explain away."** He and others point to lab data showing that amyloid can be toxic to brain cells. They note that rare inherited gene mutations that seem to cause Alzheimer's disease by raising amyloid levels. **"The evidence for amyloid is still pretty impressive,"** adds Ronald Petersen of the Mayo Clinic.

[http://www.forbes.com/2008/07/29/alzheimers-elan-pharmaceuticals-biz-healthcare-cz\\_rl\\_0729alzheimers.html](http://www.forbes.com/2008/07/29/alzheimers-elan-pharmaceuticals-biz-healthcare-cz_rl_0729alzheimers.html)

# Remember: One Year Later

- TauRx has reportedly patented a new formulation called leuco-methylthioninium or LMT, which is **no longer blue** and renders the drug more bioavailable and less toxic at higher doses (and doesn't make a patient's urine blue).
- The new formulation is presently undergoing preclinical studies.
- In the meantime, **people have been giving methylene blue to their loved ones in its form as a dye which contains heavy metal contaminants.**
- TauRx has produced a more pure substance, with low levels of heavy metal contaminants, for clinical studies.
- TauRx is also working on a **new formulation** that will not interact with the capsule, resulting in more controlled pharmacokinetics and better side effect profile.

# And Then Along Comes Dimebon: "This is too good to be true"

- Dimebon, a twenty year old Russian antihistamine being developed by San Francisco-based Medivation in partnership with Pfizer, has shocked scientists with its apparent efficacy (Forbes, July 15 2009).
- "The published paper from *Lancet* is the best thing anyone's ever seen in Alzheimer's. No one's ever seen an improvement with sustained benefit for a year, and lots of people, myself included, initially said, 'This is too good to be true,' " says Samuel Gandy, MD, PhD, professor of neurology and psychiatry at the Mt. Sinai School of Medicine, New York.

## SUMMARY OF SIX-MONTH RESULTS FROM RUSSIAN PHASE II STUDY OF DIMEBON

Endpoint	Improvement	P-value (vs. placebo)
AD Assessment Scale-cognition (ADAS-cog)	4.0 point	p<0.0001
Clinician's Interview-Base Impression of Change - plus caregiver assessment (CIBIC-plus)	0.6 units	p<0.0001
AD Cooperative Study Group - Activities of Daily Living (ADCS-ADL)	3.4 units	p=0.002
Neuropsychiatric Inventory (NPI)	3.6 points	p=0.006
Mini Mental State Exam (MMSE)	2.2 points	p<0.0001

Source: Company reports

Aricept showed 2-3 point improvement in ADAS-cog and 0.35-0.39 unit improvement in CIBIC-plus (product label)

## SUMMARY OF 12-MONTH RESULTS FROM RUSSIAN PHASE II STUDY OF DIMEBON

### SUMMARY 12-MONTH DATA FROM RUSSIAN PHASE II TRIAL OF DIMEBON

Endpoint	p-value vs. placebo <sup>a</sup>	Difference vs. placebo	p-value vs. baseline	Change vs. baseline
ADAS-cog	p<0.0001	6.9 points	NS	+1.2 points
CIBIC-plus	p=0.006	0.8 points	NS	0 points
ADCS-ADL	SS	5.2 points	NS	-0.3 points
MMSE	SS	NA	NS	+0.7 points
NPI	SS	NA	NS	-0.7 points

NS - not statistically significant

SS - statistically significant

NA - not available

Open-label extension studies of Aricept showed decline in ADAS-cog scores below their original baseline levels at ~ 9 months

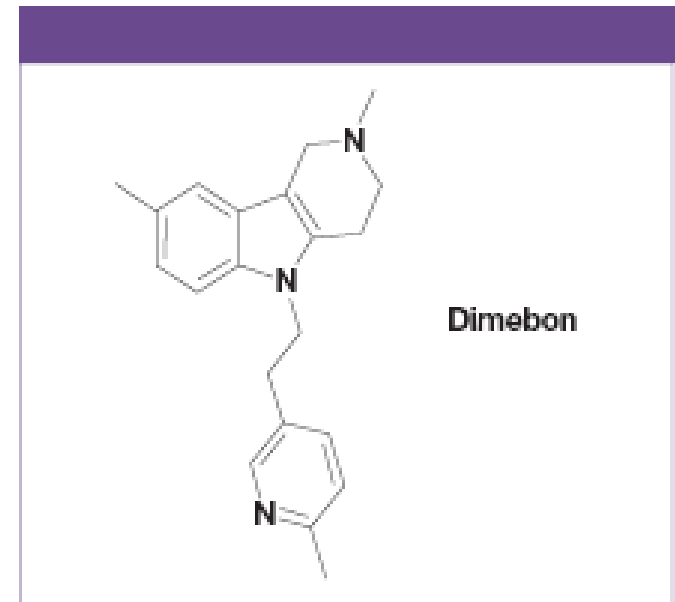
Forbes July 15, 2009; Cowen and Company Therapeutic Categories Outlook Sept. 2009

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Alzheimer's Insight Briefing

**DefinedHealth**  
unconventional insight

# How Does Dimebon Work?

- Dimebon's exact mechanism in AD is unclear, but the drug may work as:
  - (1) A cholinesterase inhibitor, albeit a relatively weak one;
  - (2) An NMDA receptor antagonist;
  - (3) A neurite outgrowth inducer; and/or
  - (4) A mitochondrial permeability transition pore (MPTP) blocker.



# Pfizer Grabs it Up

In September 2008, Pfizer gained marketing rights to Dimebon (for AD and Huntington's) giving Medivation a healthy \$225 million in upfront cash, potential future milestone payments of \$500 million or more, plus 40% of any profits on Dimebon if approved in the U.S. and royalties on its sales elsewhere in the world. Medivation will be responsible for 40% of the U.S. development and commercialization expenses.

Drug	ADAS-cog score improvement over placebo (higher is better)	Sales data, last fiscal year
Medivation and Pfizer's Dimebon	4.0 mean improvement after 26 weeks	Still in development
Elan (NYSE: <a href="#">ELN</a> ) and Wyeth's (NYSE: <a href="#">WYE</a> ) bapineuzumab	2.3 average improvement after 78 weeks	Still in development
Eisai's and Pfizer's Aricept	Between 2.8 and 3.1 mean improvement after 24 weeks	\$2.7 billion
Forest Labs' (NYSE: <a href="#">FRX</a> ) Namenda	Between 1.5 and 2.0 mean improvement after 28 weeks	\$830 million
Novartis' Exelon	Between 0.2 and 4.9 mean improvement after 26 weeks	\$630 million
Johnson & Johnson's (NYSE: <a href="#">JNJ</a> ) Razadyne	Between 3.1 and 4.1 mean improvement after 26 weeks	\$225 million

Sources: IMS Health, companies' most recent 10-K or 20-F, and study results (selected studies, not all studies included). Bapineuzumab study results for modified intent-to-treat population only; Razadyne study results for extended-release (ER) formulation.

<http://www.fool.com/investing/general/2008/09/05/why-pfizer-made-an-interesting-blockbuster-bet.aspx>

# Is Dimebon Amyloid Theory's "Herod"?

- Evidence presented at the International Conference on Alzheimer's Disease (ICAD) in July 2009 suggests that Dimebon enhances the release of amyloid- $\beta$  in three different cell and animal models of Alzheimer's.
- "The media pounced on this surprising news. Scientists, too, scratched their heads, wondering what the results mean for the amyloid hypothesis of AD, where most drug developers, including Medivation's pharma partner Pfizer, mostly try to decrease  $A\beta$  with their experimental medicines." (Tom Fagan, alzforum.org).



Forbes July 15, 2009; Alzforum.org

# Amyloid is *Not Dead Yet*

- Those who doubt the amyloid hypothesis of AD might see vindication of sorts in a drug that seems to slow the progression of cognitive decline in AD while increasing brain A $\beta$ . But the two may not necessarily be mutually exclusive.
- Sam Gandy (Mount Sinai) suggests that Dimebon may be protective because it helps remove A $\beta$  from inside neurons, where it may do most the damage.
- Andy Protter, of Medivation, does not see the A $\beta$  effect as an issue for Dimebon. “The ambiguity in what it means certainly fits with ambiguity of what A $\beta$  does in the brain,” he said. “There’s a lot of confusion about what we expect drugs to do and how we want them to do it.”
- Rachelle Doody (Baylor College of Medicine) sees no relation between Dimebon’s acute effects on A $\beta$  release and the A $\beta$  hypothesis. “In no way does this negate the A $\beta$  hypothesis, and it does not negate Dimebon,” she said.

I'm not dead yet!

Forbes July 15, 2009; Alzforum.org; Monty Python

# Amyloid Has Staying Power

## 6 of 11 Rock Stars of Science Work in Amyloid

Joining other scientific luminaries: Harold Varmus, Eric Topol, Anthony Fauci, David Agus and Francis Collins.



**Dale Schenk**



**Ron Peterson**



**Rudy Tanzi**



**Sam Gandy**



**Jeffrey Cummings**



**Steven DeKosky**

**Rock S.O.S. is a philanthropic effort to accelerate science by designer menswear brand GEOFFREY BEENE.**

# BAPTist or TAUist, the Path of Righteousness is Not an Easy One

Disease modification (DM) can be defined as treatments or interventions that **affect the underlying pathophysiology** of the disease and **have a beneficial outcome** on the course of Alzheimer's disease.

Significant questions remain in terms of:

- Trial design?
- Clinical endpoints?
- Validated biomarkers?
- Time of intervention?

# DM = Neuroprotective and Neurorestorative Approaches

In this classification both neuroprotective therapies and neurorestorative interventions would be disease-modifying.

## **Disease-Modifying (DM)**

### **• Neuroprotective**

- **Amyloid-based treatments**
- **Tau-based therapies**
- **Antioxidants**
- **Anti-inflammatory agents**
- **NMDA-receptor antagonists**
- **Apoptosis-related agents**

### **• Neurorestorative**

- **Nerve growth factor-related**
- **Stem cell-related**

# What is *Not* Disease Modification

A drug or other intervention that only delays the symptoms of AD does not adequately capture all dimensions of what is intended by *disease modification*.

- Treatment with symptomatic agents can delay important disease milestones such as progress from mild cognitive impairment (MCI) to dementia of the Alzheimer's type without affecting associated biomarkers that measure the impact on basic AD pathology.
- Studies of Aricept (donepezil) lasting for up to 2 years indicate that symptomatic agents might exert long-term benefit compared with placebo treatment by delaying disease course and resetting the course to a delayed, but parallel, decline (Figure).

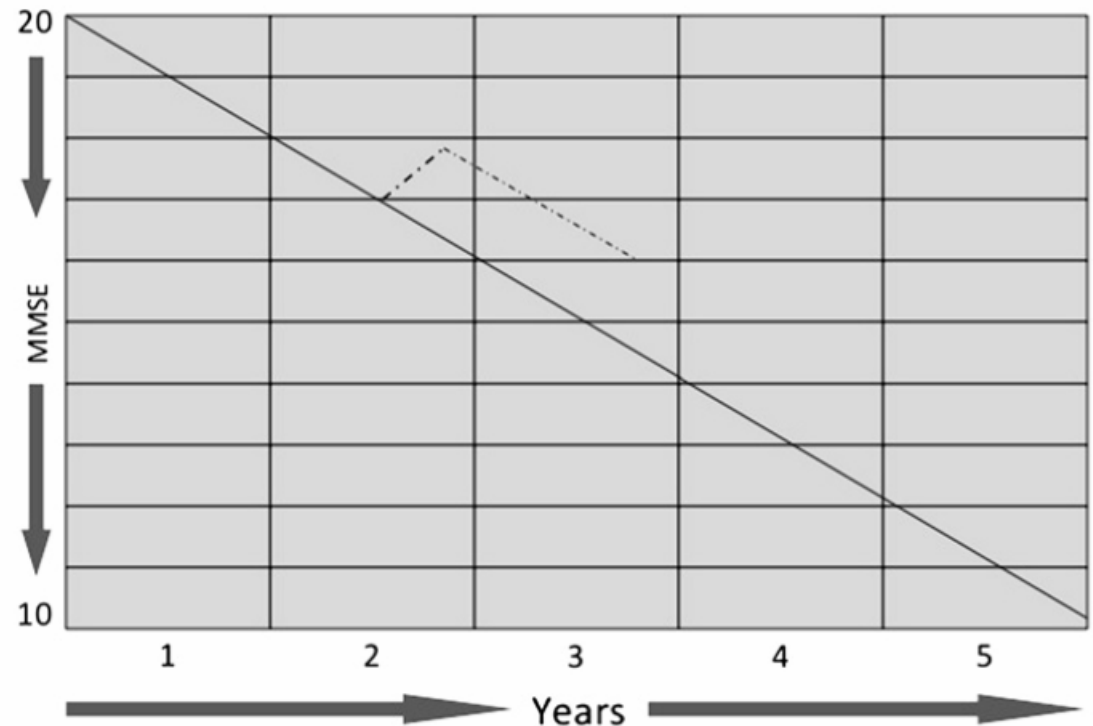


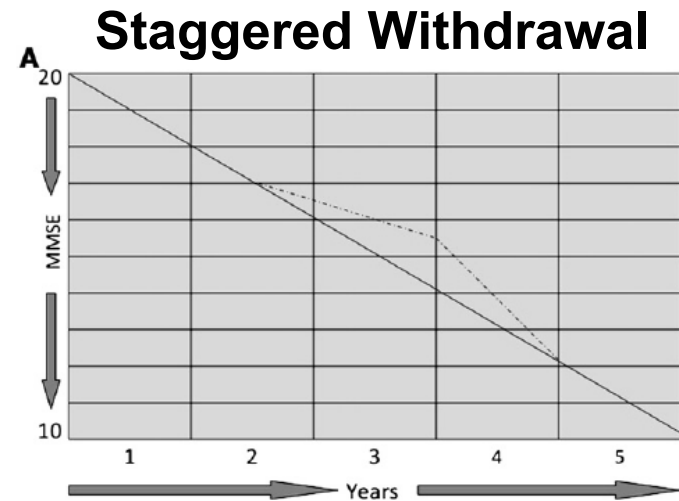
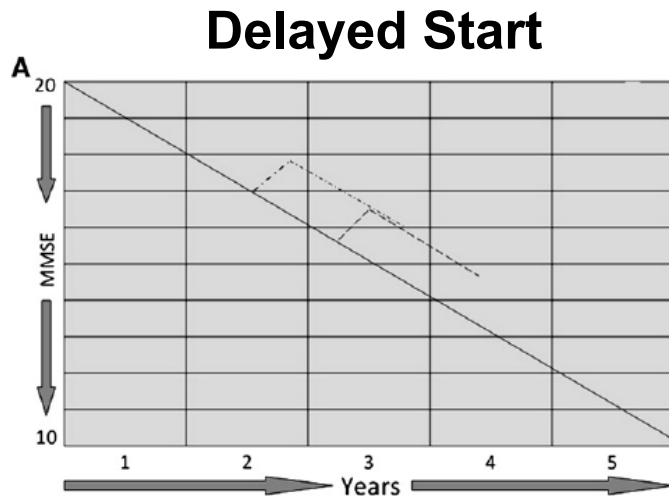
Fig. 1. Decline in AD (solid line) and the impact of treatment with a symptomatic agent (dashed line).

Cummings, J.L., Alzheimer's & Dementia 5 (2009) 406-418; Sampaio, C. J Nutr Health Aging 2006; 10:113-5; Courtney, c. et al. Lancet 2004; 363: 2105-15.

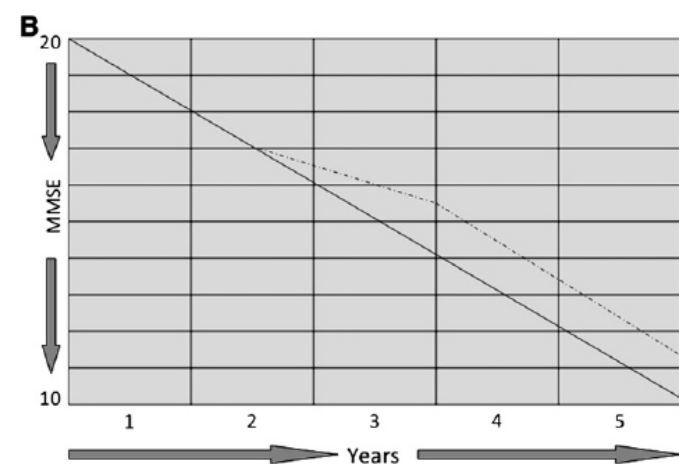
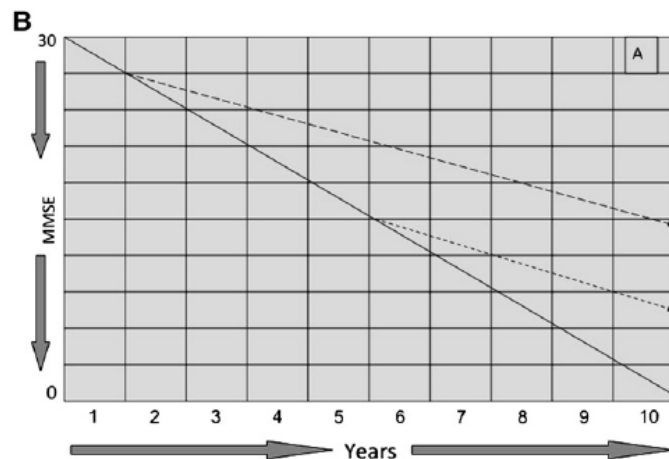
# Meeting the Criteria for DM: Fun with Trial Design

Two clinical trial designs have been identified as demonstrating disease modification, the staggered withdrawal and delayed start designs.

No DM



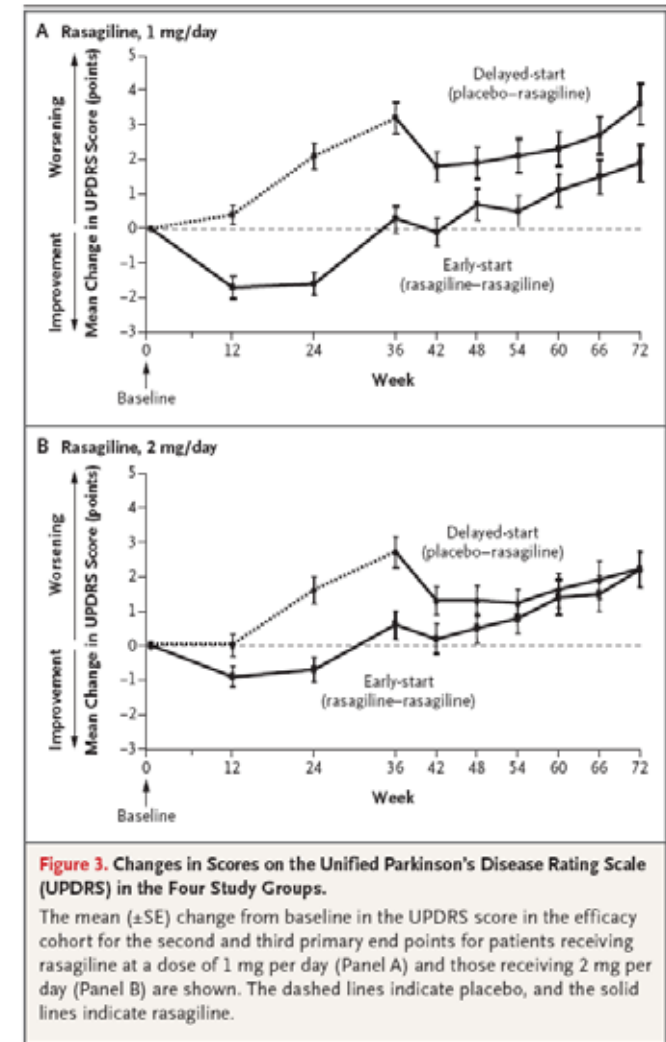
DM



# Azilect Wins with a Delayed Start Design

A trial of rasagiline (Azilect, Teva/Lundbeck) used the delayed start design and demonstrated that patients with Parkinson's disease did not catch up on the Uniform Parkinson's Disease Rating Scale (UPDRS) during the second phase of the trial.

- One of the largest Parkinson's disease studies demonstrates benefit of early treatment with Azilect® 1 mg/day.
- H. Lundbeck A/S' (Lundbeck) partner Teva Pharmaceuticals Industries Ltd. (Teva) today announced that results from the ADAGIO trial, published online today in The New England Journal of Medicine, demonstrated that Parkinson's disease patients receiving Azilect® (rasagiline) 1mg/day at the start of the study (early-start group) experienced superior benefit over 18 months compared with those who started the exact same treatment nine months later (delayed-start group)(1).
- This finding is consistent with a possible disease-modifying effect for Azilect® 1 mg/day.



NEJM 361;13 nejm.org september 24, 2009; Teva/Lundbeck press release

# Azilect Could be the First \$Billion Drug for Parkinson's

- Results from ADAGIO were first released in August 2008 at the European Federation of Neurological Societies meetings. However, the fact that the data has been published should allow for Teva to take a more aggressive posture in its marketing and may provide another inflection point in Azilect's use.
- Teva has indicated it intends to go for a disease-modifying labeling with the FDA. However, industry analysts believe that a positive outcome is rather unlikely. A decision is not expected before H2 2010. Azilect worldwide sales were \$175MM (+46%) in 2008. Sales grew to over \$240 M in 2009 and are expected to rise to \$360MM in 2012, with the ultimate potential to be a \$B product – a first for PD.

## Most Recent Azilect Weekly Trends

Azilect	20-Jun-08		17-Jul-09		24-Jul-09		31-Jul-09		7-Aug-09		14-Aug-09		21-Aug-09		28-Aug-09		4-Sep-09	
	TRx	NRx	TRx	NRx	TRx	NRx	TRx	NRx	TRx	NRx	TRx	NRx	TRx	NRx	TRx	NRx	TRx	NRx
	3,561	1,195	4,946	1,643	4,710	1,531	4,923	1,568	4,931	1,615	4,847	1,535	4,966	1,584	4,943	1,629	5,062	1,622

*ADAGIO topline results released*

Source: Cowen and Company and IMS Data

# Alzheimer's is Proving to Be More Difficult

Although promising, several aspects of these trial designs make them difficult to implement in practice for Alzheimer's studies.

- Lack of certainty as to how long the first treatment period should be.
- Unclear how long the second treatment period should last to enable a disease-modifying inference.
- If there is no drug-placebo difference at the end of the first period, then there can be no such difference at the end of the second period, and the second part of the study would be futile.
- Attrition over the course of the trial.

# DM Requires Effect on Clinical Course and a Biomarker

- This design incorporates a standard, “back to basics” parallel group study comparing drug and placebo at study conclusion.
- A treatment benefit on disease course would be supported by differences in cognitive, functional, or global outcomes at the conclusion of the trial.
- An effect on the underlying disease pathology would be established by showing a difference in the progression of biomarker measures of disease progression in the same patient group.
- In addition, a statistically significant correlation should be demonstrable between the clinical outcome and the biomarker outcome.

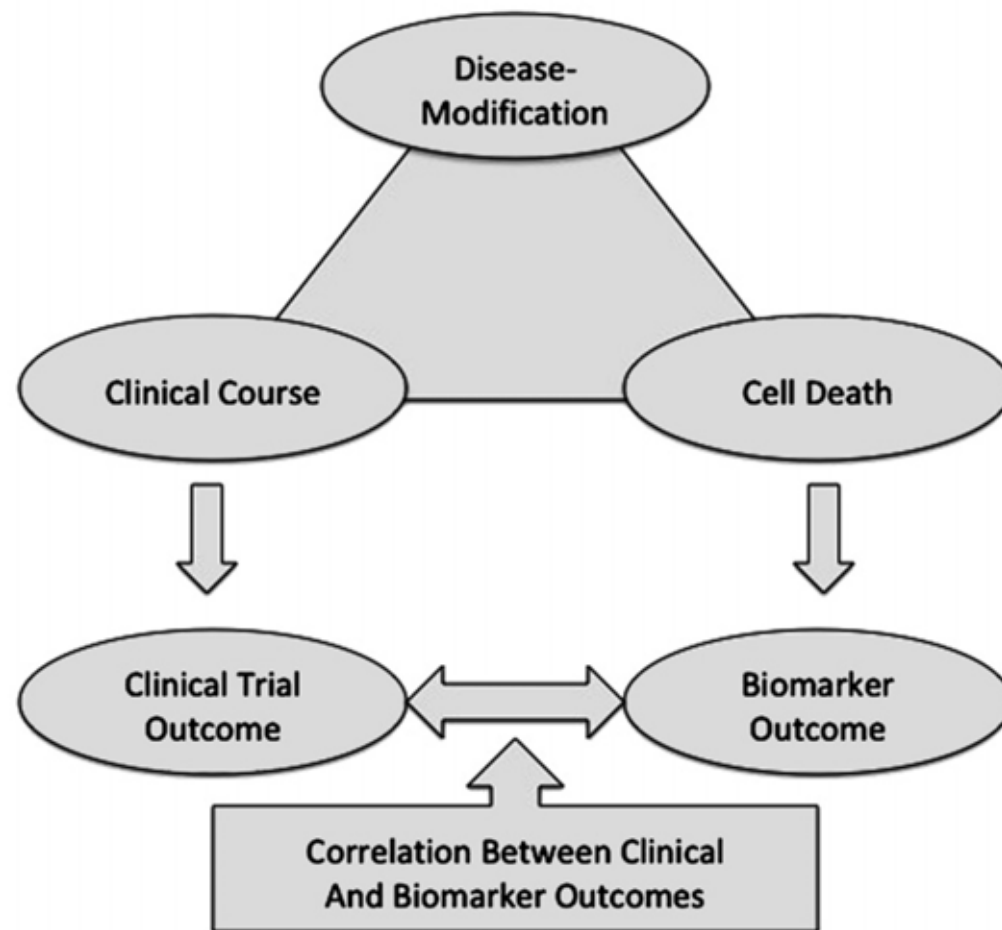


Fig. 4. Elements required to establish disease modification.

# The Problem:

There are no biomarkers that have been validated as surrogate measures for clinical outcomes in AD.

- Thus, no biomarker can be used as a substitute for a clinical outcome measure in an AD pivotal therapeutic trial.
- A variety of biomarkers have been nominated as candidates for roles in disease-modifying trials of AD therapies.
  - Magnetic resonance imaging (MRI) measures of whole brain atrophy, ventricular enlargement, or medial temporal atrophy (MTA);
  - Fluorodeoxyglucose (FDG) positron emission tomography;
  - Positron emission tomography (PET); Pittsburgh Compound B (PIB);
  - CSF measures of A $\beta$ , total tau, or hyperphosphorylated tau (p-tau); and
  - Plasma or CSF proteomic, metabolomic, genomic or transcriptomic measures

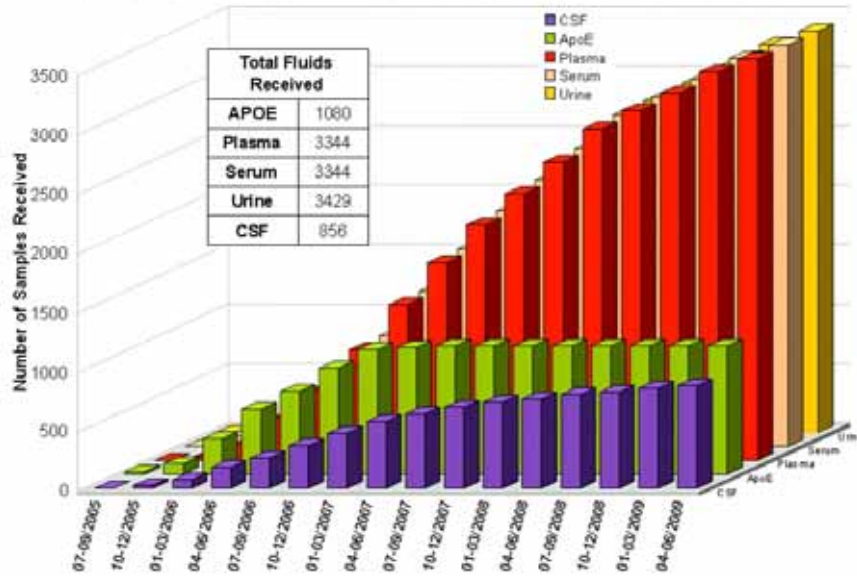
# Alzheimer's Disease Neuroimaging Initiative (ADNI)



- Collaboration between NIH, academia and pharma to advance establishment of clinical biomarkers for AD research and drug development.
- ADNI was created in an environment where there is:
  - Low power of clinical measures for disease progression and modification
  - Need for highly standardized biomarkers that provide direct evidence of disease and can monitor disease progression and modification
- Public funding drives public sharing of ADNI research results
  - ~\$100 million total funding over 6 years, 2004-2010 (70% from public sources)
- Focused on the measurement of amyloid (Abeta 42 peptide) and tau/phosphotau in biofluids, as well as neuroimaging studies

# Alzheimer's Disease Neuroimaging Initiative (ADNI)

More than 12,000 Biofluid Samples Received



## 57 ADNI sites

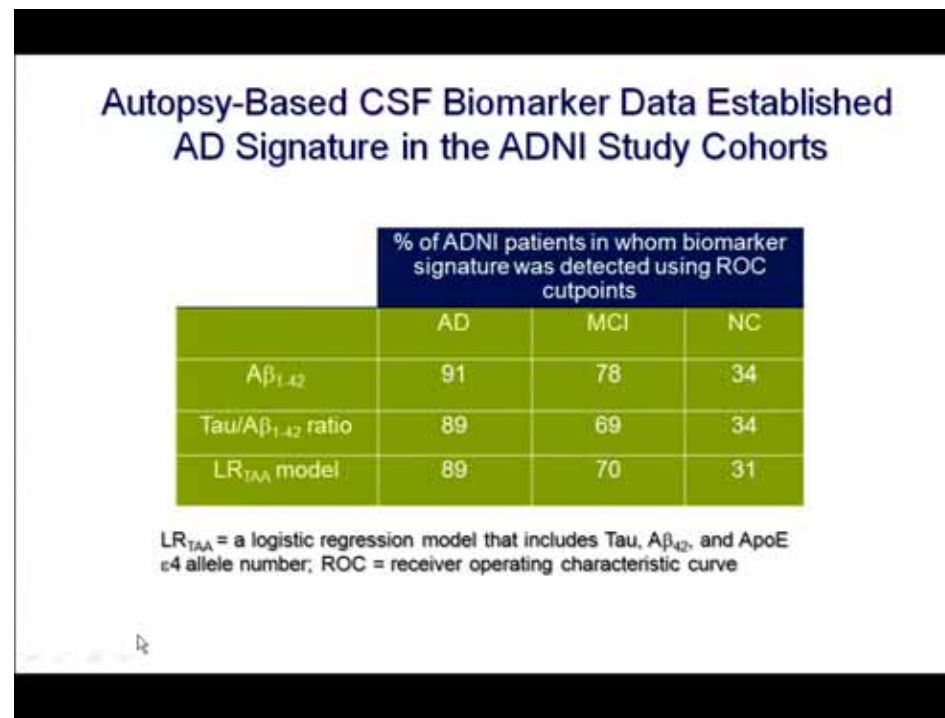
### ADNI Participating Sites



Shaw, L., Neurodegenerative Diseases  
Research Retreat Oct. 2009 Presentation

# ADNI is Delivering

- Initial (one year) data from the ADNI was presented at the April 2009 American Academy of Neurology (AAN) meeting and demonstrated a high correlation between CSF Abeta levels in mild AD patients and cognitive decline within 1-2 years.
- This finding should enable the screening of patients for clinical studies based on CSF Abeta levels to enrich for subjects patients with a high probability of cognitive decline within the trial period.
- The ADNI findings should also enable the testing of beta amyloid targeting agents in earlier-stage AD patients.



Shaw, L..., Neurodegenerative Diseases Research Retreat Oct. 2009 Presentation; SG Cowen Therapeutic Categories Outlook

# Bapineuzumab is the Frontrunner as a DM Therapy



Bapineuzumab is Phase III humanized version of murine monoclonal antibody that recognizes N-terminal of A $\beta$  that is being studied as a potential treatment for mild to moderate Alzheimer's disease.

Bapineuzumab is believed to prevent beta-amyloid aggregation and facilitate the clearing of beta-amyloid plaques from the brain via glial cells.

Bapineuzumab is delivered via an intravenous infusion once every three months.

Bapineuzumab has received fast-track designation from the FDA, and may receive expedited approval in recognition of its potential to address the significant unmet needs of patients with Alzheimer's disease.



# Followed Closely by Several Other DM Hopefuls

- Solanezumab, passive A $\beta$  vaccine (Phase III, Eli Lilly)
- LY450139, semagacestat; gamma secretase inhibitor (Phase III, Eli Lilly)
- GAMMAGARD, IVIG (Phase III, Baxter)
- ELND-005 ( $\beta$  amyloid aggregation, Phase II, Elan/Transition Therapeutics)

2010/2011 is the year for amyloid to  
make its mark – or not

# But Bapineuzumab Has Had Some Stumbles

Data for the Phase II (18-month, 240-patient) trial of the monoclonal antibody bapineuzumab for the treatment of mild-to-moderate Alzheimer's disease (AD) were released at the 2008 International Conference on Alzheimer's Disease (ICAD) meeting, causing a flurry of controversy and speculation.

***06 / 17 / 2008 press release***

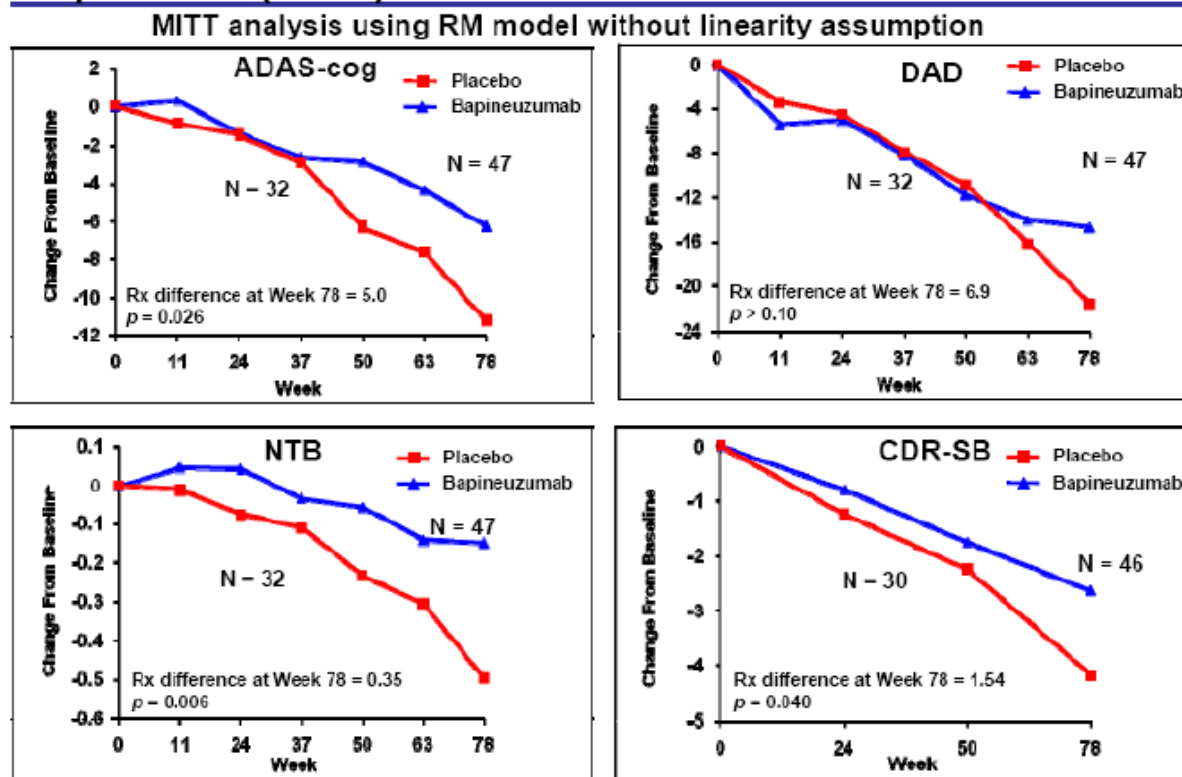
- **Elan and Wyeth Announce Encouraging Top-line Results from Phase 2 Clinical Trial of Bapineuzumab for Alzheimer's Disease**
  - ***Safety And Efficacy Findings Support Design Of Phase 3 Program***
  - ***Primary Efficacy Endpoints In Overall Study Population Not Statistically Significant***
- ***Statistically Significant And Clinically Meaningful Benefits Seen In ApoE4 Non-Carriers***
- ***Overall Results Support Prior Decision To Initiate Phase 3***
- ***Detailed Data Presentation At ICAD July 29, 2008***

# Bapineuzumab Shows Significance in Post Hoc Analysis

The overall study population did not reach statistical significance on the primary efficacy endpoints. However, when the data was analyzed post-hoc by apolipoprotein E (ApoE) genotype, patient responses divided into two groups:

- 1) Statistically Significant and Clinically Meaningful Benefits Seen In ApoE4 Non-Carriers
- 2) ApoE4 Carriers Showed No Statistically Significant Efficacy on Any of the Endpoints and Experienced Significantly Higher Adverse Events (vasogenic edema being the most concerning).

## Clinical Efficacy Endpoints: ApoE4 Non-carrier Population (MITT)



Source: ICAD presentation

# Apolipoprotein E as a Predictor of Alzheimer's

There are three major isoforms of apolipoprotein E (apoE), namely apoE2, apoE3, and apoE4, that are products of three alleles ( $\epsilon 2, \epsilon 3, \epsilon 4$ ) at a single gene locus on chromosome 19. It is well known that the presence of apoE4 increases the risk for the development of Alzheimer's disease and atherosclerosis.

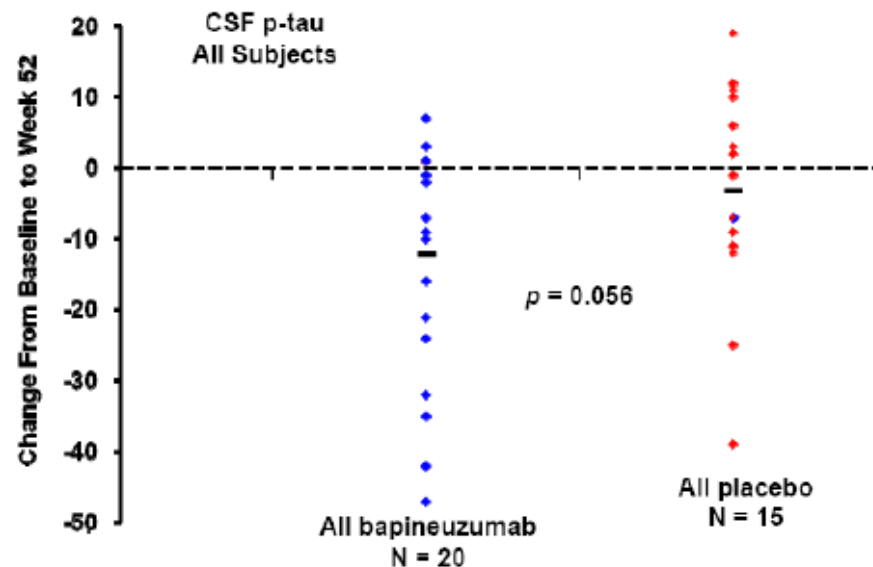
- Patients with two ApoE4 alleles are 15 times as likely to develop AD than those with non-ApoE4 alleles; age of onset is about a decade earlier than those with non-E4 alleles.
  - ApoE4/4 patients start forming plaques as early as their 40's (some 15 years before symptoms are present), and, therefore, are thought to reach a critical amyloid plaque burden at an earlier point in life.
  - Throughout the spectrum of the disease, ApoE4 patients have more severe pathology in terms of the major markers of the disease, including:
    - Amyloid angiopathy
    - Tau pathology, and
    - Vascular pathology (cerebrovascular lesions).
- ApoE4 is less efficient in its role of facilitating the clearance of soluble amyloid beta peptide ( $A\beta$ ) in the brain.
- An estimated 50% of AD patients do not carry the ApoE4 allele.

# Bapineuzumab Biomarker Evidence is Confounding

There was a trend toward lowering CSF phosphorylated tau (p-tau), although the reduction did not reach statistical significance. There was no observed change in A $\beta$  levels in the CSF, which was somewhat unexpected for a drug designed to target beta-amyloid.

## CSF Biomarkers

- Phospho-tau (p-tau) levels trend lower at 52 weeks in bapineuzumab-treated patients versus placebo-treated patients
- No differences in CSF A $\beta$  or total tau



Based on ANCOVA; one outlier excluded in the 0.15 mg/kg placebo dose cohort

Source: ICAD presentation

ICAD presentation; SG Cowen Therapeutic Categories Outlook

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Alzheimer's Insight Briefing

# Nevertheless, Phase III Will Go On

- Bapineuzumab will be studied in two separate Phase III trials using an “enrichment” design to optimize chance of success: 1) ApoE2 and 3 carriers (ApoE4(-)) in a study administering higher doses of bapineuzumab, and ApoE4 carriers (ApoE4(+)) in a study administering a lower dose intended to reduce the likelihood of vasogenic edema.

## BAPINEUZUMAB PHASE III PROGRAM

	U.S. ApoE4(-) trial	U.S. ApoE4(+) trial	Int'l ApoE4(-) trial	Int'l ApoE4(+) trial
Total patients	1,250	800	1,250	800
Study duration	18 months	18 months	18 months	18 months
Dose groups/doses	4 (0.5, 1.0, 2.0mg/kg, placebo)	2 (0.5mg/kg, placebo)	4 (0.5, 1.0, 2.0mg/kg, placebo)	2 (0.5mg/kg, placebo)
Patients/dose group	313	400	313	400
Primary endpoints	(ADAS-cog or NTB), (DAD or CDR)	(ADAS-cog or NTB), (DAD or CDR)	(ADAS-cog or NTB), (DAD or CDR)	(ADAS-cog or NTB), (DAD or CDR)
Secondary endpoints	(ADAS-cog or NTB), (DAD or CDR)	(ADAS-cog or NTB), (DAD or CDR)	(ADAS-cog or NTB), (DAD or CDR)	(ADAS-cog or NTB), (DAD or CDR)

Source: [clinicaltrials.gov](http://clinicaltrials.gov), Company reports

Source: [Clinicaltrials.gov](http://Clinicaltrials.gov); Company reports; SG Cowen analyst report  
 Alzheimer's Disease Assessment Scale (ADAS-cog), Neuropsychological Test Battery (NTB), Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR). Disability Assessment Scale for Dementia (DAD)

# Elan, Wyeth Abandon Top Dose of Bapineuzumab

Thu Apr 2, 2009

LONDON, April 2 (Reuters) - Irish drugmaker Elan (ELN.I) and U.S. partner Wyeth WYE.N are to **stop testing the highest dose of their experimental Alzheimer's drug, bapineuzumab, due to safety concerns.**

The news wiped some 7 percent off Elan shares on Thursday on fears that patients in final-stage clinical trials might be reluctant to continue taking other doses.

The decision to discontinue the 2.0 mg/kg dose in the studies follows a review of cases of **vasogenic edema**, or the build-up of fluid in the brain.

"Our review of the safety data and the feedback from the Safety Monitoring Committee made it clear that continued development of the highest dose was not advisable," Elan President Carlos Paya said.

Testing of the 0.5 mg/kg and 1.0 mg/kg doses in two Phase III trials will continue as planned.

Reuters Press Release

# The Phase II Conundrum

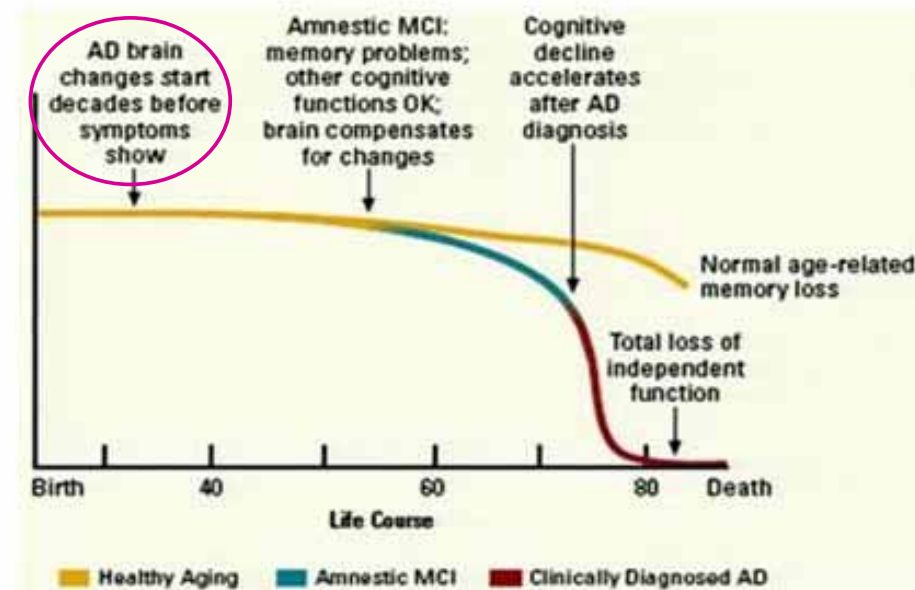
- **Development of disease modifying drugs represents a particular challenge to the usual temporal sequence of drug development.**
  - The Phase II bapineuzumab trial was 18 months in 240 patients.
- The Phase II Conundrum: How little data can be used to form an adequate platform in Phase II for launching a Phase III trial.
  - Advancing to Phase III with inadequate Phase II data increases the likelihood of failure.
  - Abandoning a drug after a negative Phase III trial, when there has been inadequate dose finding in Phase II, may result in overlooking potentially beneficial drugs.
- Potential contributing solutions for the Phase II conundrum include:
  - Development of biomarkers that are more responsive and can serve in place of clinical measures or at least assist in drug development decisions.
  - Development of more sensitive clinical measures that will reflect drug activity in smaller populations or in shorter trials.
  - The use of clinical trial designs that may shorten Phase II (such as adaptive designs).
    - Adaptive clinical trial designs allow alterations in dose, population, or endpoint after the initiation of the trial.
  - Legislative relief to extend patent protection for disease-modifying compounds.

Cummings, J.L. International Review of Psychiatry, August 2008; 20(4): 389-395

# Will Trial Design Even Matter if the Intervention is Too Late?

A major concern for bapineuzumab, as well as other disease modifying therapies in development, is that treatment is being introduced too late in the course of the disease.

- Even in the earliest stages of AD (Mild Cognitive Impairment), the brain has a full load of amyloid which has been building over decades and, up to the point of symptoms, has been innocuous.
- Neuroimaging studies show very little increase in amyloid burden between the MCI and AD proper stages of the disease; therefore the damage may already be done.
- The bapineuzumab trials include patients with mild-moderate AD, which is probably not the optimal point to target the disease.



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# AD is Complicated; It May Be Time for a Polytheist Society: BAPtists and TAUists working together?

PNAS

Nov. 6, 2009  
Early Online Edition

## Amyloid- $\beta$ and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice

Virginie Rhein<sup>a</sup>, Xiaomin Song<sup>b</sup>, Andreas Wiesner<sup>c</sup>, Lars M. Ittner<sup>c</sup>, Ginette Baysang<sup>a</sup>, Fides Meier<sup>a</sup>, Laurence Ozmen<sup>d</sup>, Horst Bluethmann<sup>d</sup>, Stefan Dröse<sup>a</sup>, Ulrich Brandt<sup>a</sup>, Egemen Savaskan<sup>a,f</sup>, Christian Czech<sup>d</sup>, Jürgen Götz<sup>c,g</sup>, and Anne Eckert<sup>a,1</sup>

<sup>a</sup>Neurobiology Laboratory for Brain Aging and Mental Health, Psychiatric University Clinics, University of Basel, 4025 Basel, Switzerland; <sup>b</sup>Australian Proteome Analysis Facility, Macquarie University, Sydney NSW 2109, Australia; <sup>c</sup>Alzheimer's and Parkinson's Disease Laboratory, Brain and Mind Research Institute, University of Sydney, 100 Mallett Street, Camperdown NSW 2050, Australia; <sup>d</sup>Hoffmann-La-Roche AG, Pharma Research, Neurosciences, 4070 Basel, Switzerland; <sup>e</sup>Molecular Bioenergetics Group, Medical School, Cluster of Excellence Frankfurt Macromolecular Complexes, Center for Membrane Proteomics, Johann Wolfgang Goethe-Universität, 60590 Frankfurt am Main, Germany; <sup>f</sup>Division of Psychiatric Research and Hospital for Psychogeriatric Medicine, University of Zurich, 8032 Zurich, Switzerland; and <sup>g</sup>The Medical Foundation, University of Sydney, Camperdown NSW 2050, Australia

(AD) is characterized by amyloid-beta ( $A\beta$ )-containing plaques, neurofibrillary tangles, and neuron and synapse loss. Tangle formation has been reproduced in P301L tau transgenic pR5 mice, whereas APPswPS2N141I double-transgenic APP152 mice develop  $A\beta$  plaques. **Cross-breeding generates triple transgenic (tripleAD) mice that combine both pathologies in one model.** To determine functional consequences of the combined  $A\beta$  and tau pathologies, we performed a proteomic analysis followed by functional validation. Specifically, we obtained vesicular preparations from tripleAD mice, the parental strains, and nontransgenic mice, followed by the quantitative mass-tag labeling proteomic technique iTRAQ and mass spectrometry. Within 1,275 quantified proteins, we found a massive deregulation of 24 proteins, of which one-third were mitochondrial proteins mainly related to complexes I and IV of the oxidative phosphorylation system (OXPHOS). Notably, deregulation of complex I was tau dependent, whereas deregulation of complex IV was  $A\beta$  dependent, both at the protein and activity levels. Synergistic effects of  $A\beta$  and tau were evident in 8-month-old tripleAD mice as only they showed a reduction of the mitochondrial membrane potential at this early age. At the age of 12 months, the strongest defects on OXPHOS, synthesis of ATP, and reactive oxygen species were exhibited in the tripleAD mice, again emphasizing synergistic, age-associated effects of  $A\beta$  and tau in perishing mitochondria. **Our study establishes a molecular link between  $A\beta$  and tau protein in AD pathology in vivo**, illustrating the potential of quantitative proteomics.

# He is a Rock Star to Me



Alzheimer's & Dementia 2 (2006) 147-149

## Perspectives

Finding potent drugs for Alzheimer's disease is more important than proving the drugs are disease modifying

David Knopman\*

*Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA*

Knopman, D. Alzheimer's & Dementia 2 (2006) 147-149

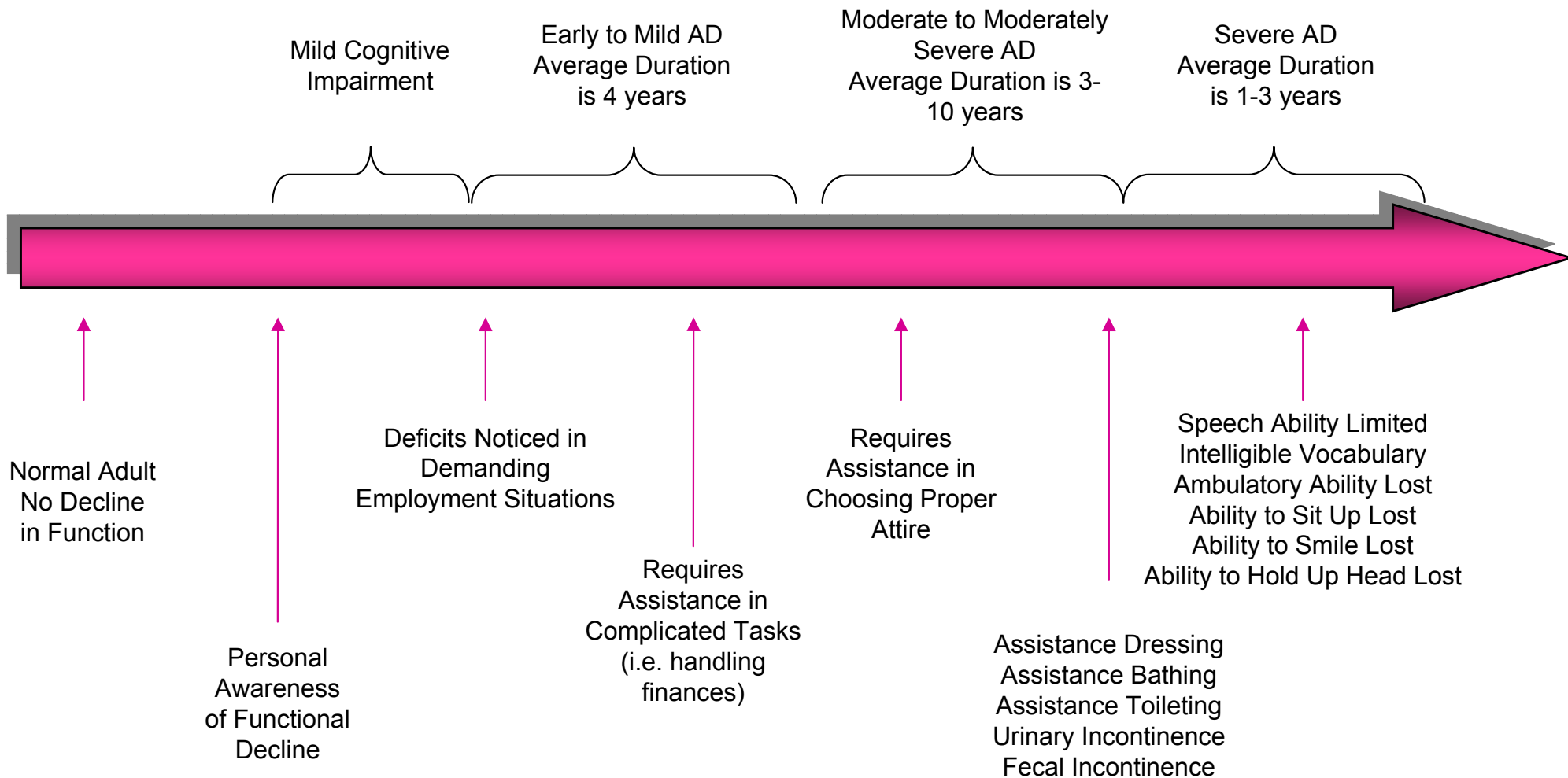
# There is Still Plenty of Room For Symptomatic Improvement

- Simple and efficient designs have intrinsic appeal that outweighs many benefits of gaining a DM indication.
- Simple designs of shorter duration have the potential to test interesting compounds more expeditiously.
- From a patient and family perspective, “I believe that a drug that was not DM but that had substantially more potent impact on the symptoms of the disease than the currently available agents would be very well received.”

Knopman, D. Alzheimer's & Dementia 2 (2006) 147-149

# But That Benefit Must Make a Difference to the Patient

At some point in the progression of the disease, it is of no benefit to the patient (and the caregiver) to be “a little less demented”. We need to really move the needle.



Source: Alzheimer's Association

# In Conclusion...

- There is a tremendous and exploding need in AD.
- Efforts should progress on all fronts.
- Applaud those advancing the field – underlying biology, trial design, biomarkers, etc.
- It is time for the BAPtists and TAUists to work together.
- DM is the holy grail, but incremental benefits are important.
- The next big thing in AD may be clinically-meaningful improvement of symptomatic therapy.



**Defined Health's Therapeutic Insight will be a featured track at these 2010 EBD conferences:**

**BIO-Europe Spring® 2010**  
March 8–10, 2010  
Barcelona, Spain

**BIOPharm America® 2010**  
September 15–17, 2010  
Boston, MA