The changing diagnostic criteria for AD, including early and asymptomatic disease stages and their impact on clinical trial design

Eric Siemers
On behalf of the EFPIA Working Group

24-25 November 2014
London UK

European Federation of Pharmaceutical Industries and Associations
www.efpia.eu

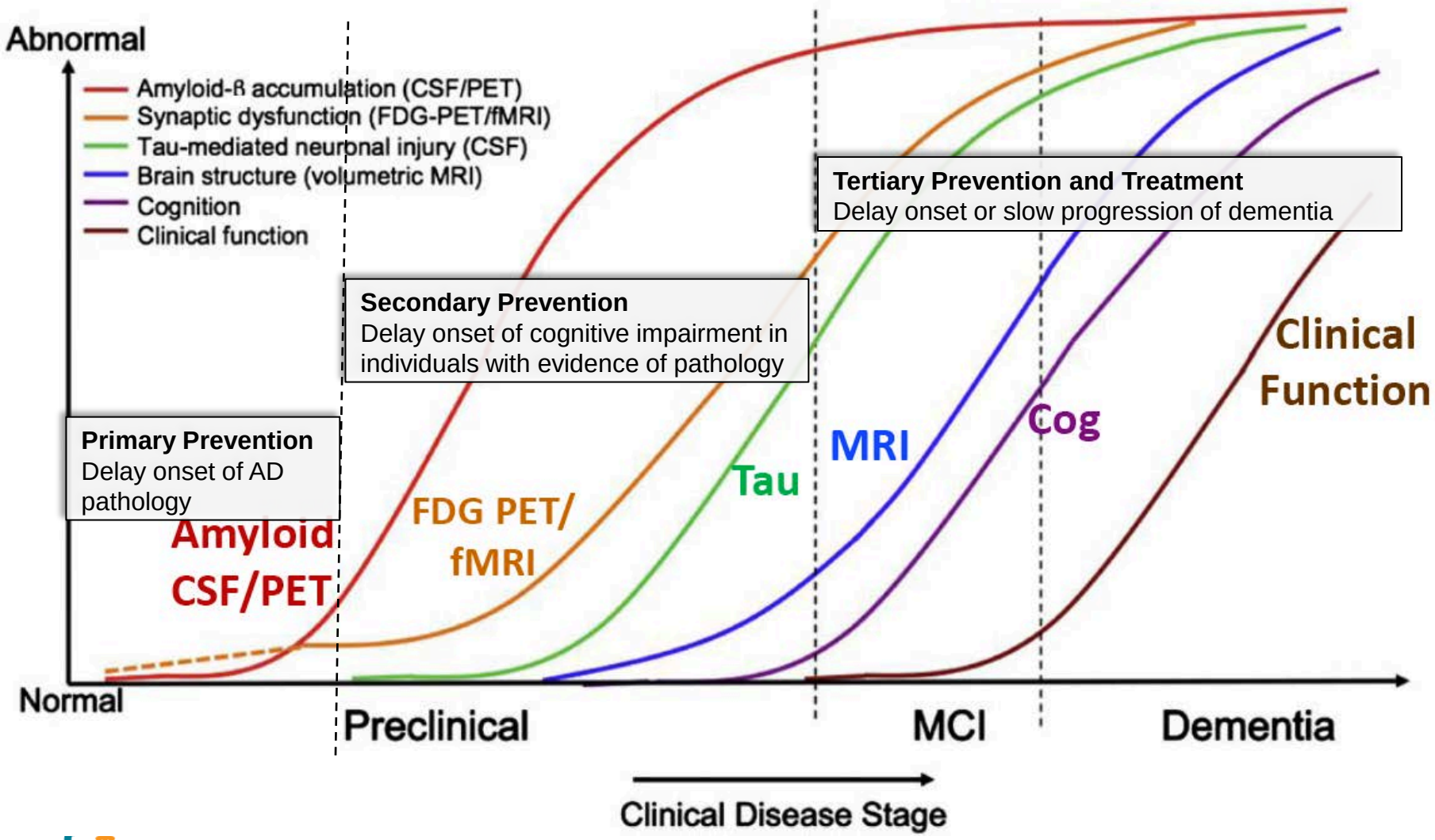
Disclosure

- Eric Siemers MD is a Distinguished Medical Fellow, employee and shareholder at Eli Lilly and Company

Our understanding of AD pathology and clinical symptoms have improved substantially

- Amyloid plaques form 10-20 years prior to the onset of AD dementia
- The ordering of other biomarker changes including CSF tau through the course of preclinical and clinical AD is becoming better understood
- The relationship of different domains of clinical symptoms (e.g. cognition and function) is becoming better understood

AD pathology begins prior to the onset of clinical symptoms



Clifford Jack et al. Lancet. Neurol. 2010 January; 9(1): 119.
Reisa Sperling, Clifford R Jack, Paul S Aisen Science translational medicine Nov 2011

Refining clinical trial designs for putative disease-modifying therapies

Alzheimer's disease progression

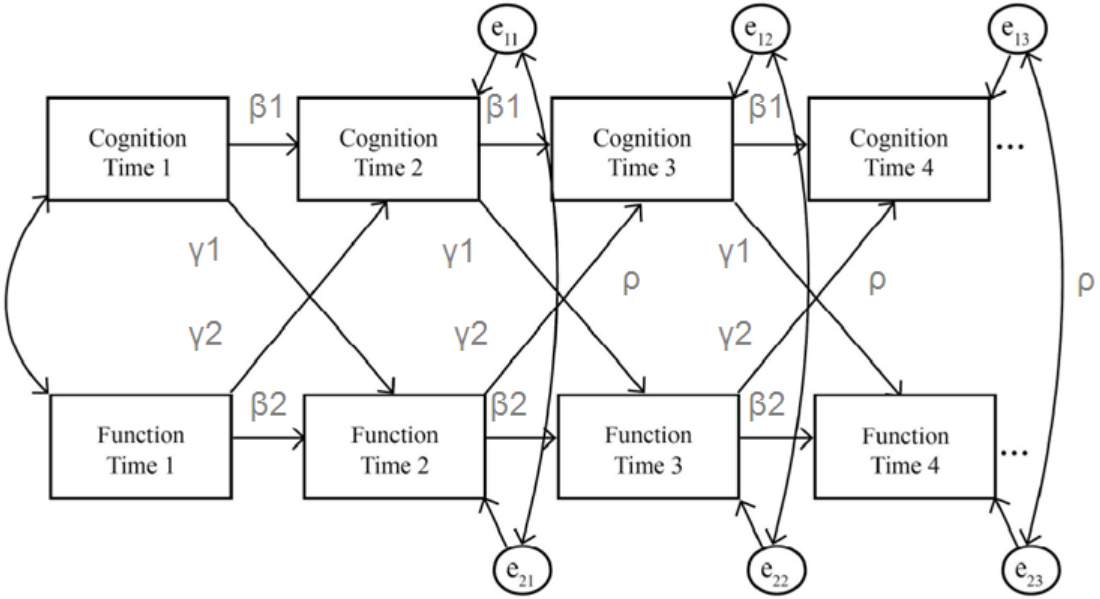
Preclinical	Prodromal	Mild	Moderate	Severe

- Definitions of the preclincial, prodromal and mild populations are operationalized for clinical trials
- Appropriate outcome measures will need to be established for each group of patients
- The clinical differences between patient groups will not be distinct for clinical trial populations, and will be even less distinct in clinical practice.

efpia

The relationship between cognitive and functional domains is becoming better understood

A Path Diagram Describing the Interrelationship Between Bivariate Longitudinal Data



Adapted from Zahodne et al. 2013. Copyright: © 2013 Zahodne et al.

Overall model fit assessed using comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR), which are standard measures used in panel analyses of this type.[1]
Acceptable values: CFI≥0.9, RMSEA≤0.08, SRMR≤ 0.05.[2,3]

[1]Selig and Little. Chapter 16 in : Laursen B, Little TD, Card NA (eds.). 2012. *Handbook of Developmental Research Methods*. The Guilford Press, pp265-278.
[2]Gao et al. Proceedings of SAS Users Group International 2006 meeting (SUGI31), Paper 187-31.
[3]Zahodne et al. PLOS ONE 2013; 8(9): e73645

efpia

ARCL Panel Analysis Results Predictors Study

	Predictor of Function (γ1)	Predictor of Global Cognitive Status (γ2)
	Estimate (SE)	Estimate (SE)
Visit 1	-0.15** (0.03)	-0.14** (0.03)
Visit 2	-0.17** (0.03)	-0.05 (0.03)
Visit 3	-0.16** (0.03)	-0.06* (0.03)
Visit 4	-0.14** (0.03)	-0.07* (0.03)
Visit 5	-0.20** (0.03)	0.02 (0.03)
Visit 6	-0.07* (0.03)	-0.05 (0.03)
Visit 7	-0.15** (0.03)	-0.00 (0.03)
Visit 8	-0.18** (0.04)	0.01 (0.03)
Visit 9	-0.13* (0.04)	0.03 (0.03)
Visit 10	-0.15* (0.05)	0.00 (0.03)
Visit 11	-0.25** (0.05)	0.03 (0.05)

* $p<.05$, ** $p<.001$

Abbreviations: CFI=comparative fit index; RMSEA=root mean square error of approximation; SE=standard error; SRMR=Standardized root mean square residual

- Model fitting statistics

	Model Value	Desired Value
RMSEA	0.04	<0.08
SRMR	0.03	<0.05
CFI	0.98	>0.95

- Cross-lagged regression coefficients significant 11/11 for predictor of function, while 3/11 for predictor of cognition.
- Stronger cross-lagged coefficient for cognition predicting subsequent function than vice versa
- Data support functional impairment is a direct result of cognitive impairment

Source: Zahodne et al. PLOS ONE 2013; 8(9): e73645

efpia

Ongoing trials are studying cohorts earlier in the course of AD

			pre-clinical	prodromal	mild	moderate
Phase 2	BAN2401	Eisai			ADCOM	
	Crenezumab	Genentech	API		ADAS+ADL	
Phase 3	MK8931	Merck		CDR-SB	ADAS+ADL	
	Ganteneurmab	Roche	DIAN	CDR-SB	ADAS+ADL	
	Solanezumab	Lilly	A4/DIAN		ADAS+ADL	

efpia

Diagnostic Criteria

- 1906: Dr. Alois Alzheimer discovered amyloid plaques and neurofibrillary tangles in a patient
- Until recently, a confirmatory diagnosis required clinical features and histopathological confirmation by brain biopsy or autopsy

Matthews and Miller. In: *The Behavioral Neurology of Dementia*, 2009.
Photographs used with permission.

Our diagnostic classification systems have evolved based on new information

- **NINCDS-ADRDA criteria**, 1984[1]
  - Based on correlation between pathology and clinical symptoms
  - Did not incorporate nonamnestic presentations, biomarker information, or concept of MCI
  - Clinical focus and diagnosis of exclusion
- **International Working Group (IWG): New research criteria for diagnosis of AD**, 2007[2]
  - Included early/prodromal stages of AD; incorporated biomarker information, and memory impairment
  - Formalized the idea of a continuum; becomes a diagnosis of inclusion
- **IWG research criteria: New lexicon for AD**, 2010[3]
  - Attempt to provide a common language about disease stages and types of evidence
  - Distinguished MCI from prodromal and incorporated atypical presentations
- **NIA/AA criteria**, 2011[4]
  - Written to address both research and clinical practices
  - Formalized different stages of continuum: preclinical AD, MCI due to AD, AD dementia
  - Incorporated adjunctive biomarker information to the criteria
  - Includes atypical presentations
- **DSM-5 criteria**, 2013[5]
  - Terminology shift from dementia to neurocognitive disorders (NCDs)
  - Major or mild NCD subtypes can be due to Alzheimer's disease

1. McKhann G et al. *Neurology* 1984;34(7):939-44.
2. Dubois B et al. *Lancet Neurol* 2007;6(8):734-46.
3. Dubois B et al. *Lancet Neurol* 2010;9(11):1118-27.
4. Jack CR Jr et al. *Alzheimers Dement* 2011;7(3):257-62.
5. American Psychiatric Association. DSM-5, 2013.

IWG Recommendations for Revised Research Criteria for AD Diagnosis

	AD Diagnosis	Presence of Impairment on Specified Memory Tests	Evidence of AD Biomarkers *In Vivo*	Additional Requirements
Typical AD	Yes	Required	Required	None
Atypical AD	Yes	Not required	Required	Specific clinical presentation
Prodromal AD	Yes	Required	Required	Absence of dementia
AD dementia	Yes	Required	Required	Presence of dementia
Mixed AD	Yes	Required	Required	Evidence of comorbid disorders
Asymptomatic at-risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
MCI	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

Dubois B et al. *Lancet Neurol* 2010;9(11):1118-27.

NIA/AA Criteria: Staging Categories for AD Including Biomarkers

Category	Subcategory	Amyloid[a] (PET or CSF)	Neuronal Injury[a] (tau, FDG, MRI)	Cognition/Function
Preclinical[1]	Stage 1	Positive	Negative	Asymptomatic
	Stage 2	Positive	Positive	Asymptomatic
	Stage 3	Positive	Positive	Subtle cognitive/behavioral decline
MCI due to AD[2]	Intermediate Likelihood	Positive	Untested	• ≥1 cognitive domains impaired, typically memory • Atypical presentations possible • Mild functional impairment but remain independent • Not demented
		Untested	Positive	
	High Likelihood	Positive	Positive	
	Unlikely	Negative	Negative	
AD Dementia[3]	Probable; Intermediate Likelihood	Positive	Unavailable/ indeterminate	<u>Amnestic</u> • Learning and recall impaired plus ≥1 other cognitive domain • Insidious onset <u>Nonamnestic</u> • ≥2 domains impaired: language, visuospatial, or executive • Insidious onset
		Unavailable/ indeterminate	Positive	
	Probable; High Likelihood	Positive	Positive	
	Possible; High Likelihood Doesn't R/O 2nd Etiology	Positive	Positive	Atypical (sudden onset, or insufficient history/evidence of progressive decline) or mixed etiology dementia
	Unlikely	Negative	Negative	Typical or atypical AD dementia

[a]Recommended for research purposes in preclinical and MCI stages; biomarkers can be used to increase certainty of diagnosis in dementia stage in research and when needed and appropriate in clinical setting

1. Sperling RA et al. *Alzheimers Dement* 2011;7(3):280-92.
2. Albert MS et al. *Alzheimers Dement* 2011;7(3):270-9.
3. McKhann GM et al. *Alzheimers Dement* 2011;7(3):263-9.

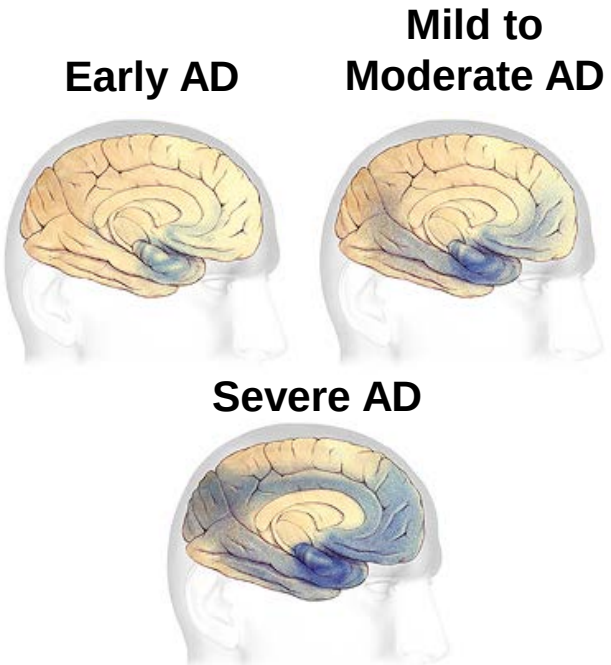
DSM-5 Criteria for Major and Mild Neurocognitive Disorder due to AD

Type and Degree of Clinical Impact	Major NCD	Mild NCD
A. Concern by individual, informant, or clinician of *cognitive decline* from previous performance	Significant cognitive decline	Mild cognitive decline
B. *Cognitive impairment* – based on standardized neuropsychological testing or another qualified clinical assessment	Substantial cognitive impairment	Modest cognitive impairment
C. Involves *cognitive domains*: complex attention, executive function, learning/memory, language, perceptual-motor, or social cognition	≥2 cognitive domains	≥1 cognitive domains
D. Impairment insidious in onset; gradually progresses	Same	Same
E. Cognitive deficits and *interference* with activities of daily living ADLs and instrumental ADLs (iADLs)	Does interfere with ADLs and with complex iADLs	Does NOT interfere with ADLs; may interfere with iADLs
F. Clinical features must not suggest another primary etiology	Same	Same

American Psychiatric Association. DSM-5, 2013.

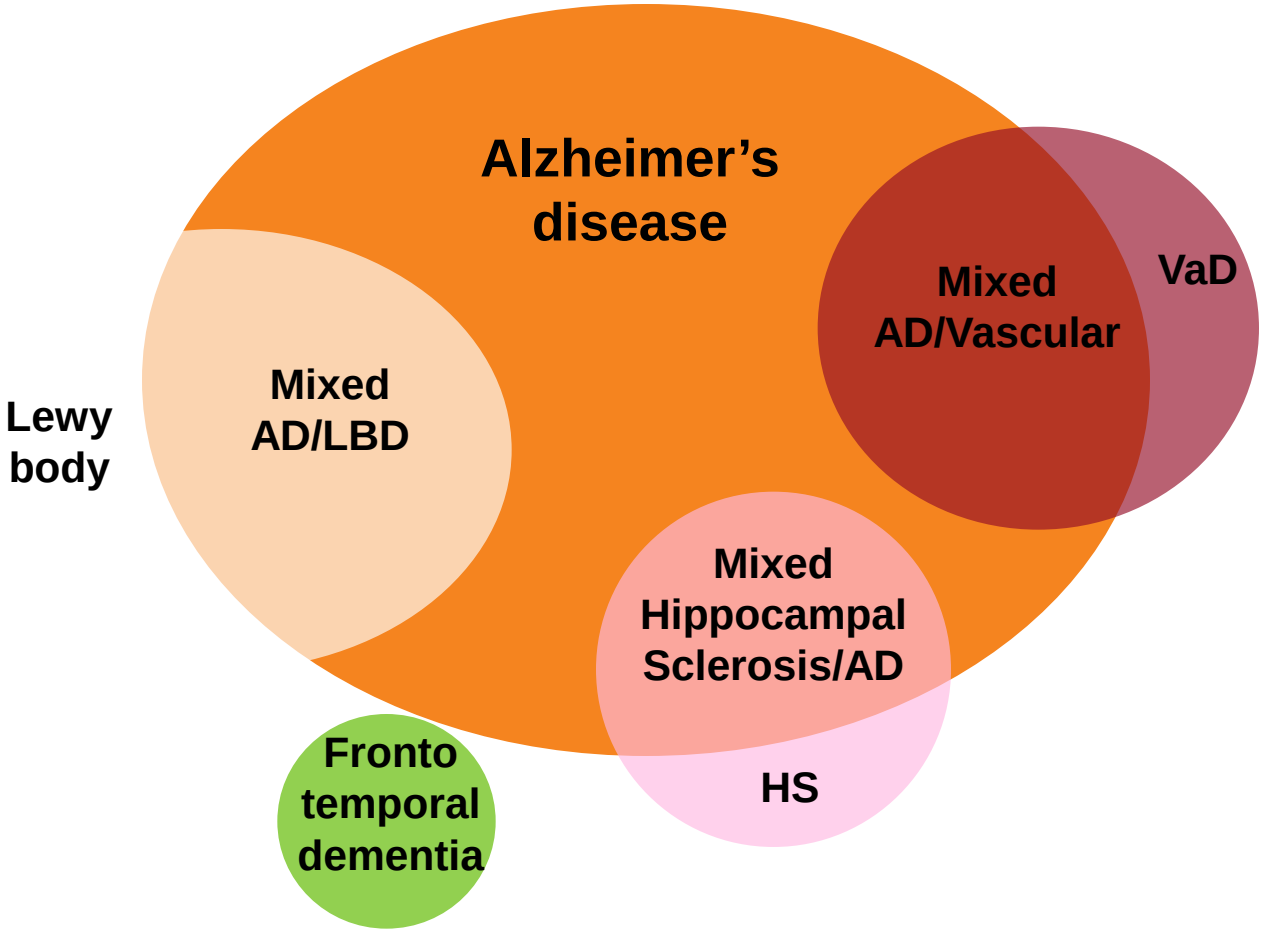
Comparison of Recent Diagnostic Terminology for Alzheimer's Disease Stages

- No or subtle complaints
  - IWG: asymptomatic or presymptomatic AD[1]
  - NIA/AA: preclinical AD[2]
- Mild stage (cognitive impairment with preservation of functional independence)
  - IWG: prodromal (has biomarker evidence of AD)[1]
  - NIA/AA: mild cognitive impairment (etiology uncertain without biomarker)[3]
  - DSM-5: mild neurocognitive disorder due to AD[4] (possible; probable with causative genetic mutation)
- Dementia stage (impairment in daily living)
  - IWG: AD dementia[1]
  - NIA/AA: dementia due to AD (possible or probable)[5]
  - DSM-5: major neurocognitive disorder due to AD (probable AD)[4]



1. Dubois B et al. *Lancet Neurol* 2010;9(11):1118-27.
2. Sperling RA et al. *Alzheimers Dement* 2011;7(3):280-92.
3. Albert MS et al. *Alzheimers Dement* 2011;7(3):270-9.
4. American Psychiatric Association. DSM-5, 2013.
5. McKann GM et al. *Alzheimers Dement* 2011,7(3):263-9.
6. http://www.alz.org/braintour/progression.asp.

Diagnostic criteria for AD may need modification for mixed pathologies



Adapted from Barker et al. *Alzheimer Dis Assoc Disord* 2002;16(4):203-12.

Key regulatory questions (1/2)

- Based on recent biomarker and other data, we conclude that Alzheimer's disease is a continuum, and the operationally defined stages of disease are not clearly demarcated. Does the agency agree?

Key regulatory questions (2/2)

- Based on the concept of a continuum of AD, and the similarities between prodromal AD and mild AD dementia as defined operationally, we conclude that these populations can be combined into a single cohort (‘early AD’) for the purpose of clinical trials. Does the agency agree?
  - Based on extensive work supporting the use of a single composite outcome for trials in prodromal AD, we conclude that such a measure could also be an appropriate primary outcome for a trial investigating patients with prodromal AD and mild AD dementia (‘early AD’). Does the agency agree?

EFPIA Brussels Office

Leopold Plaza Building
Rue du Trône 108
B-1050 Brussels - Belgium
Tel: +32 (0)2 626 25 55

www.efpia.eu