ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

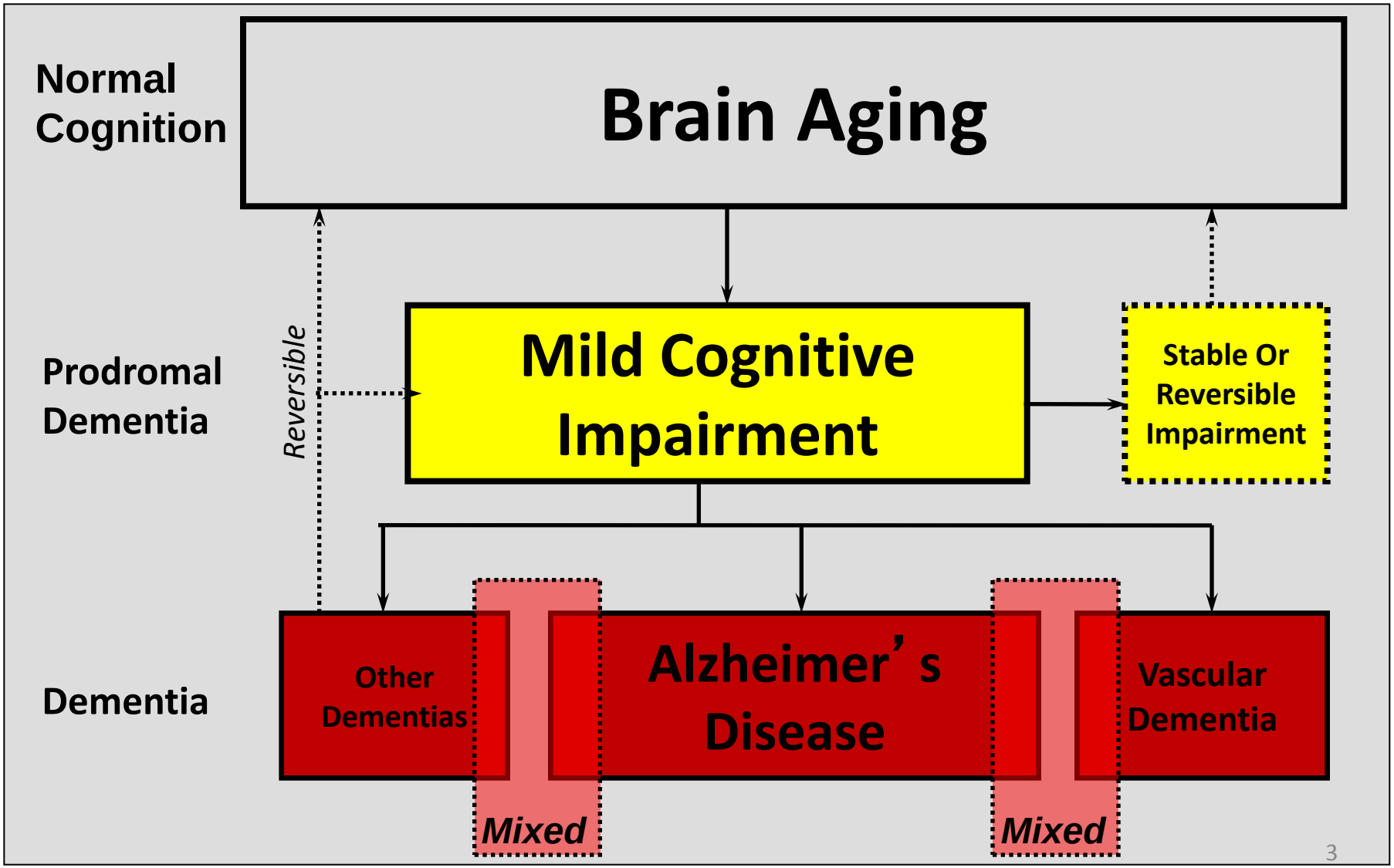
Regulatory Challenges across Dementia Subtypes – European View

- Population definition including Early disease "at risk"
- Endpoints in POC studies
- Endpoints in pivotal trials

Disclaimer

- No CoI
- The opinions expressed are personal opinions and do not necessarily reflect the official views of the Federal Institute of Drugs and Medical Devices (BfArM) or the European medicines Agency (EMA).

MCI is Prodromal Dementia



Revision of Diagnostic Criteria for Alzheimer´s Disease

- **NINCDS-ADRDA** (McKhann1984): clinical criteria of probable AD for the dementia stage of AD with evidence of cognitive **and** functional impairment (DMS-IV and ICD 10)
- **IWG** critera (Dubois 2007,2010 and 2014 (in press)): clinicobiological criteria of prodromal and preclincial AD
- **NIH-AA** criteria (Albert 2011) : MCI due to AD

Research criteria

- DMS-5 : major and mild neurocognitive disorder

Albert et al 2011, Dubois et al 2007 , 2010 and 2014 (in press) , McKhann et al 1984 and 2011, Sperling et al 2011

AD as Clinicobiological Entity

Phenotype	Biology
Typical – Amnestic syndrome of the hippocampal type **Atypical** – Posterior cortical atrophy – Logopenic variant – Frontal variant **Asymptomatic at risk** – No specific phenotype (typical or atypical) **Presymptomatic** – No specific AD phenotype (typical or atypical)	CSF (low Aβ and high tau) OR Amyloid PET (high retention of amyloid tracer) AD related autosomal dominant mutation (in PSEN1,PSEN2, or APP)

EMA Guidance

- Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias **(CPMP/EWP/553/95 Rev. 1)**

- Draft concept paper on need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias **(EMA/CHMP/61773472013)**

http://www.ema.europa.eu

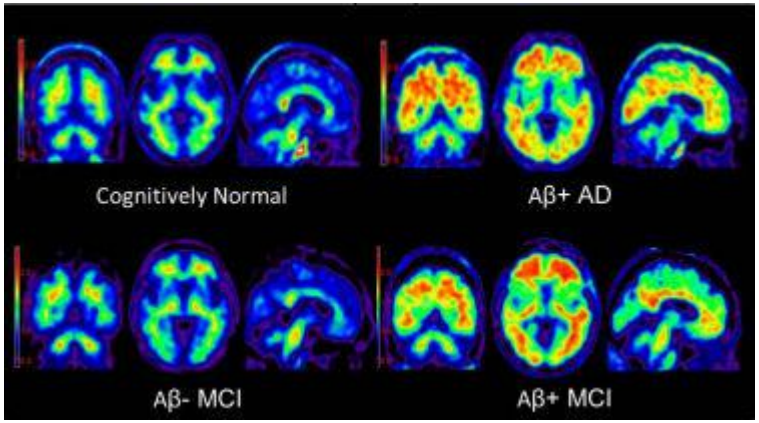
Three Major issues for recent and future clinical trial protocols in AD and other Dementias

- New research citeria for different stages of AD
- The potential use of biomarkers in different stages of drug development
  - **Diagnostic** – for determining diagnosis
  - **Enrichment** – for reinforcing entry criteria
  - **Prognostic** – for determining course of illness
  - **Predictive** – for treatment outcomes
- The use of appropriate outcome measures with adequate clinical relevance to be used at any stage of the disease continuum

Dynamic Biomarkers

Biomarkers of brain amyloid β (A β) accumulation

- CSF β-Amyloid I-42
- PET amyloid imaging



Biomarkers of neuronal degeneration or injury

- CSF total-τ-Protein and phospho-τ-Protein increase
- Hypometabolism on fluorodeoxyglucose PET (FDG)
- Atrophy on structural MRI

Biomarkers that suggest that the MCI syndrome is unlikely due to AD

- Loss of dopamine transporters in SPECT (DLB)
- Extensive cerebrovascular disease (VaD)
- Frontal or frontotemporal hypometabolism, hypoperfusion or atrophy (FTD)

Such biomarkers are not as well established as for AD.

Critical Issues

- **Sensitivity and specificity of diagnostic criteria:** e.g. moderate sensitivity and **high specificity** for the IWG criteria with a diagnostic accuracy of 93-100%
- **Biomarker performance** (precision, replicability, validity, positive and negative predictive value for each purpose)
- **Biomarker operationalization** (cut-off scores, sensitivity and specificity for e.g. AD)

Efficacy
(Symptomatic Improvement in mild to moderate Dementias)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance:
  proportion of patients with meaningful benefit ?

Duration of treatment: at least 6 months

Standard clinical trial design: DB, placebo-controlled, parallel group, dual outcome approach, add-on designs

- **secondary endpoints**
  - global domain
  - additional symptoms, e.g. agitation

Efficacy
(Disease Modification)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance:
  proportion of patients with meaningful benefit ?
- Duration of treatment: **18 months (?)**
- **secondary endpoints**
  - global domain
  - Biomarkers
    - e.g. serial volumetric MRI
  - Quality of Life
  - additional symptoms

Scales/Endpoints

- **Cognition**
  - ADAS-Cog (with further items? e.g. ADAS-Cog-Plus, adaptation to e.g. VaD)
  - Severe Impairment Battery (SIB)
  - Neuropsychological Test Battery (NTB)
  - *Clinical Dementia Rating Sum of Boxes (CDR-SB)*
- **Functional**
  - Alzheimer Disease Cooperative Study ADL Scale (ADCS-ADL)
  - Instrumental activities of daily living (IADL)
  - Alzheimer‘s Disease Functional Assessment and Change Scale (ADFACS)
  - Disability Scale in Dementia (DAD)
  - Nurses Observation Scale for Geriatric Patients (NOSGER)
  - *Clinical Dementia Rating Sum of Boxes (CDR-SB)*
- **Global**
  - CIBIC-plus
  - ADCS-CGIC

Scales should be standardized for use in different languages and cultures.

Set of instruments is encouraged rather than composite scores.

Specific considerations for other Dementias

- In **DLB** divergence of slopes (change with respect to time) might be difficult to measure. Assessment of fluctuation of symptoms is considered to be of high importance (CAF).
- **VaD** might not progress as rapidly – longer trials required, NINDS-AIREN criteria

Issues with trials in early phase

- **Clinical Endpoints of interest may be difficult to use**
  - Not sensitive enough
  - Requirement of co-primary endpoints not feasible
  - Long follow-up measurement
  - **…..**

Biomarkers the way out?

- **Surrogate (replacement) Endpoint**
  - Easier/quicker to measure
  - Reduce trial duration, size and expenditures
  - Should be measured accurately and reproducible
  - Change in proportion to what it represents

Regulatory view: still no sufficiently validated surrogates for phase III pivotal studies in patients with Alzheimer's disease available!

- **Cerebrospinal fluid markers (e.g. phospho-τ ⬆ and β-Amyloid I-42 ⬇)**
  - helpful as trait markers with high sensitivity and specificity
  - yet no value as state markers
- **Brain imaging (e.g. MRI of medial temporal lobe)**
  - helpful as trait markers for enrichment of populations at risk
  - serial MRI helpful as state marker
  - can be used as endpoint in dose finding
  - proof of concept studies
  - as secondary endpoint in pivotal studies
- **Brain imaging (e.g. PET-amyloid imaging or regional glucose metabolism)**
  - helpful as trait marker
  - yet no value as state marker

EMA Qualification Opinion on CSF and PET Biomarker signature

- CSF biomarker signature based on a low Aβ1-42 and a high T-tau
- and Amyloid related positive/negative PET signal

  qualify to identify patients with clinical diagnosis of

  a) mild to moderate AD who are at increased risk to have an underlying AD neuropathology,

  b) predementia AD who are at increased risk to have an underlying AD neuropathology

  for the purposes of enriching a clinical trial population.
- The concurrent assessment of other qualified biomarkers in the predementia state of AD would be highly desirable and of greatest value.
- **Not** qualified as diagnostic tool or outcome or longitudinal measure

EMA/CHMP/SAWP/893622/2011
EMA/CHMP/SAWP/102001/2011
EMA/CHMP/SAWP/862414/2011

Novel Study Designs

Disease modification/ prevention

- Larger phase 2 studies
- Combined phase 2/phase 3 study
- **Staggered start and delayed withdrawal designs**
- **Targeted design:** select study population based on genotype, cognitive status , biomarker
- **Adaptive designs:** - biomarker adaptive threshold design (establishment of cut point)
  - adaptive signature design
- Time-to-onset designs
- Futility designs
- Combination therapy designs

Conclusions

- It is useful to enrich trials with biomarkers.
- Amyloid positivity is a useful marker for identifying persons with amyloid pathology but other potential surrogates should be explored.
- It is similarly important to study patients who lack those markers.
- New trial designs, including adaptive and targeted designs, should be explored.
- In the absence of reliable biomarker surrogates, very sensitive measures of cognition may be the most robust indicator of efficacy in pivotal phase 3 trials.
- Harmonization is needed.
- Operationalized criteria across dementia subtypes are needed

Vellas et al 2013

Early Involvement of SAWP – What will be offered?

- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.
- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

Thank you for your attention!

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health (BMG)