

# Alzheimer's Disease

Modernizing Concept, Biological Diagnosis and Therapy

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## Regulatory Requirements on Clinical Trials in Alzheimer's Disease

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### Abstract

Recent progress in understanding the neurobiology and pathophysiology of Alzheimer's disease (AD) has fostered new interest for more efficacious symptomatic treatments as well as for disease-modifying approaches based on these insights. This has many implications for regulatory scientific advice and decision-making. Leaving the concept of the full picture of dementia as a first step of diagnosis for AD requires new standardization of diagnostic criteria, particularly for earlier disease stages. In consequence, new validated assessment tools sensitive to change for the different dimensions of AD are necessary in early AD. If a treatment claim for disease modification is strived for, it has to be shown that the treatment has an impact on the underlying pathophysiology of AD in addition to clinical improvement. This will lead to more complex study designs (adaptive designs, staggered start and withdrawal designs, combination of symptomatic and potential disease-modifying compounds, etc.). In addition to this, progress in qualification and validation of biomarkers might play an important role in future drug development for AD. Some biomarkers are already in the process of implementation as outcome variables into regulatory guideline documents, e.g. regarding phase II in drug development programs as outcome measures in proof-of-concept or dose-finding studies. Further validation of specific biomarkers in large-scale international controlled multicenter studies is necessary before they can be accepted as outcome measures in pivotal phase III clinical trials. Unfortunately, no biomarker has been sufficiently validated to be acceptable as a surrogate endpoint. Establishing surrogate endpoints is an important goal in early AD as traditional clinical outcome measures might be too subtle to be sensitive to change or need unfeasible treatment durations for clinical trial conditions. Improvements can only be accomplished by active synergistic collaboration between academic, industrial and regulatory partners.

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Despite rapid progress in understanding the neurobiology and pathophysiology of Alzheimer's disease (AD), only several cholinesterase inhibitors and memantine have been approved for symptomatic treatment with overall limited symptomatic

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improvement, whereas for example in Parkinson's disease, longer lasting symptomatic improvement effects are much more impressive compared to AD, yet no product has been approved for disease modification in any neurodegenerative disorder by regulatory bodies. Unfortunately, many recent clinical trials have failed to show symptomatic improvement or promising hints for disease modification in AD, e.g. medicinal products with an A $\beta$ -targeted mode of action. Several reasons must be considered for these negative outcomes: the amyloid cascade hypothesis might be more important for the very early disease stages and not for patients with fully established features of dementia. Patient populations included in the clinical trials still showed a certain amount of heterogeneity and medicinal products might have been introduced to phase III programs without proper phase II testing [1–5].

The term dementia describes a syndrome characterized by memory impairment, intellectual deterioration, changes in personality and behavioral abnormalities (DSM-IV-TR, ICD-10). These symptoms are of significant severity to interfere with social activities and occupational functioning. Moreover, the observed cognitive deficits must represent a decline from a higher level of function. In general, the disorders constituting the dementia syndromes share a common symptom presentation and are identified and classified on the basis of different etiologies and pathophysiologies. However, there is now a common understanding between all stakeholders that the full picture of dementia represents an advanced disease stage, which limits the treatment options with a chance of clinically meaningful improvements. This underscores the need for new criteria of AD and its earlier disease stages.

The main goals of treatments for AD might be: (1) symptomatic improvement, which may consist mainly in enhanced cognition and improved daily functioning, more autonomy and/or improvement in neuropsychiatric and behavioral dysfunction; (2) disease modification with slowing or arrest of symptom progression of the dementing process, and (3) primary prevention of disease by intervention in key pathogenic mechanisms at a presymptomatic stage.

For symptomatic treatment the development and use of relevant reliable and sensitive instruments to measure cognition, functional and behavioral symptoms, particularly for the assessment of activities of daily living and behavioral symptoms is encouraged.

Currently there is a lack of agreement on the appropriate methodology to demonstrate slowing or arrest of the dementing process [6, 7]. Data on prevention of dementing conditions are still very limited and have been disappointing up to now. Prevention studies in AD need to be large, may last for many years and due to that must take into consideration high dropout rates. Enrichment strategies and the development of better screening and measurement tools for asymptomatic or early forms of dementia combined with biomarkers may help to gain more data in the future.

For regulatory purposes, efficacy and safety for symptomatic improvement are typically determined in at least two separate randomized, double-blind, placebo-controlled trials that are each of at least 6 months' duration [8]. As a further requirement,

efficacy must be established in a cognitive domain as well as in a functional or global domain. Statistical significant differences must be demonstrated in both primary endpoints. These co-primary clinical outcome measures are currently required for both symptomatic as well as disease-modifying approaches in pivotal phase III studies. However, taking into consideration the natural history of symptom progression in AD and depending on the hypothesized mechanism of action, attempts to establish disease modification are likely to require not only much longer study duration than for symptomatic treatment, but also alternate designs (e.g. staggered start or staggered withdrawal designs). Therefore, clinical trial designs for symptomatic therapy will be different from disease-modifying approaches [8]. Particularly in the latter case the use of biomarkers and the search for adequate surrogate endpoints is encouraged by all stakeholders involved in drug development and harmonization of views is urgently needed [9–13]. Mani [14] outlined that for a claim of disease modification by the FDA, it is required that a therapeutic intervention shows clinical improvement together with modification of the underlying pathophysiological process. Similarly, by European regulators a disease-modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition. Consequently, a true disease-modifying effect cannot be established conclusively based on clinical outcome data alone. Such a clinical effect must be accompanied by strong supportive evidence from a biomarker program [8, 15]. Some important thoughts on diagnostic criteria and the role of biomarkers from a regulatory point of view are outlined in the following.

### **Diagnostic Criteria of Alzheimer's Disease**

In our current guidance we follow the criteria for dementia and AD as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR of the American Psychiatric Association) or in ICD-10 of the WHO. The probability that a dementia syndrome is caused by AD is essentially based on a history of a steadily progressive course and on the absence of evidence for any other clinically diagnosable cause of the dementia. It can be further specified by using the NINCDS-ADRDA criteria [16]. Almost all clinical trials included patients with probable AD based on these criteria. However, we are highly interested in the ongoing efforts to establish new diagnostic criteria with special emphasis on presymptomatic and early symptomatic stages of AD.

Therefore, a few years ago, mild cognitive impairment (MCI) was proposed as a nosological entity in elderly patients with mild cognitive deficits but without the complete picture of dementia, and as such became an area of high research interest. The rationale behind the development of this term is that an individual patient will pass through a stage of impaired cognition without social or occupational impairment and

that the start of treatment in this early stage will result in greater benefits [17, 18]. This new term shows overlapping with other definitions as ‘benign senescent forgetfulness’, ‘age-associated memory impairment’, ‘age-associated cognitive decline’ and ‘cognitively impaired not demented’. However, the concept of MCI is still in progress and suffers from several limitations. Estimations of prevalence from epidemiological studies vary greatly depending on the used definitions and criteria. A high proportion of patients diagnosed with MCI returned to normal without progression to dementia, on the other hand in several studies rates of progression from MCI to the full spectrum of dementia up to 12% per year have been described. Preliminary data from clinical trials using cholinesterase inhibitors in patients with MCI have not shown efficacy in the predefined primary endpoints. Thus, MCI has not been considered as a homogeneous clinical entity for regulatory purposes and more work on characterization of meaningful diagnostic criteria is needed, particularly the multiplicity of MCI definitions, the role of etiological subtypes (e.g. amnesic type of MCI) and the development of appropriate assessment tools has to be refined [19, 20].

As members of an international workgroup, Dubois et al. [21, 22] proposed criteria that may help to clarify the MCI controversy. They offered a redefinition of AD as a dual clinico-biological syndrome that can be recognized in vivo, prior to the full onset of dementia, on the basis of (1) a specific core clinical phenotype comprised of an amnesic syndrome of the hippocampal type and (2) supportive evidence from biomarkers of the presence of AD-type biological changes (table 1). AD is diagnosed with the same criteria throughout all symptomatic phases of the disease. The criteria and definitions were further elucidated by the group in 2010 [21]. The major advantage of the Dubois/IWG criteria has been to integrate the use of biomarkers into diagnosis to allow a biologically-based approach to diagnosis independent of disease severity.

Along similar lines, another set of diagnostic criteria has been proposed recently by the National Institute on Aging and Alzheimer Association comprised work groups [23–25]: three clinically relevant diagnoses of preclinical AD, MCI due to AD, and AD dementia with a continuum between and within each stage (NIA-AA criteria). These criteria take into consideration previous clinical definitions of MCI, dementia and AD dementia and incorporate biomarkers electively into the diagnostic workup as research opportunities (table 2). This means that biomarkers are not advocated for routine clinical use for the time being, however in research environments positive biomarkers can be used to stratify patient populations into distinct subgroups with a specific risk profile for AD (up to 17 diagnostic categories).

Both approaches show important similarities and differences and clearly need further validation and standardization work before they can be considered unanimously for pivotal studies in AD. However, from a regulatory point of view, the Dubois/IWG criteria seem to be less complicated and as such more readily applicable in clinical diagnosis and more easily generalizable to everyday clinical practice. As in both approaches biomarkers are key elements for probability of a diagnosis of AD, the regulatory requirements for biomarker use in clinical trials are described.

**Table 1.** Dubois/IWG research criteria for probable AD: a plus one or more supportive features B, C, D, or E

*Core diagnostic criteria*

- A Presence of an early and significant episodic memory impairment that includes the following features:
- 1 Gradual and progressive change in memory function reported by patients or informants over more than 6 months
  - 2 Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalize with cueing or recognition testing and after effective encoding of information has been previously controlled
  - 3 The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

*Supportive features*

- B Presence of medial temporal lobe atrophy: volume loss in the hippocampus, entorhinal cortex, or amygdalae on MRI with qualitative ratings by visual scoring (referenced to well-characterized population with age norms)
- C Abnormal CSF biomarker: low amyloid  $\beta$ 1–42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three; or abnormalities in other well-validated markers that will be discovered in the future
- D Specific pattern of reduced glucose metabolism in bilateral temporal parietal regions of functional neuroimaging with PET or with other well-validated ligands, such as Pittsburgh Compound B or FDDNP (2-(1(6-[(2-[ $^{18}$ F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene) malononitrile)
- E Proven AD autosomal dominant mutation within the immediate family

**Table 2.** Biomarkers of pathophysiology in the revised NIA-AA diagnostic criteria [23–25]

*Biomarkers of brain  $\beta$ -amyloidosis*

- Increased uptake on amyloid imaging with PET\*
- Decreased CSF amyloid  $\beta_{42}$ \*

*Biomarkers of neuronal injury (synaptic dysfunction and neuronal degeneration)*

- Temporoparietal hypometabolism on  $^{18}$ F-fluorodeoxyglucose PET\*
- Medial temporal (hippocampal) atrophy\*
- Increased CSF tau/phospho-tau\*
- Temporoparietal hypoperfusion on single-photon emission CT

*Other less validated biomarkers, biomarkers of collateral damage, or serial biomarkers*

- Functional MRI activation studies, resting blood oxygen level-dependent functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging
- Inflammatory (cytokines) and oxidative stress biomarkers (isoprostanes)
- Rates of brain atrophy

NIA-AA = National Institute on Aging and the Alzheimer's Association.

\* Markers included in an early proposal for revised criteria by Dubois et al. [21, 22]