EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
EMA/CHMP/617734/2013
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias

Agreed by CNS Working Party	October 2013
Adoption by CHMP for release for consultation	24 October 2013
Start of public consultation	31 October 2013
End of consultation (deadline for comments)	31 January 2014

The proposed guideline will replace 'Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias' (CPMP/EWP/553/95 Rev. 1)

Comments should be provided using this template. The completed comments form should be sent to cnswpsecretariat@ema.europa.eu

Keywords	Alzheimer's Disease, Dementia

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

Despite of recent 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 clinical improvement in mild to moderate or severe AD. Whereas e.g. 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. The current development of drug targets and therapeutics for AD, is dominated by the conceptual framework of the amyloid cascade hypothesis which postulates that Aβ peptide deposition is an early pathological process that drives tau phosphorylation, neurofibrillary tangle formation and neuron death. Unfortunately, many clinical trials with an Aβ-targeted mode of action, failed so far to show symptomatic improvement or promising hints for disease modification in mild to moderate AD; however, in some analyses of a subpopulation with mildest forms of AD slight improvements in cognition have been reported.

Since 1984 the diagnosis of AD has been based on the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Based on this definition AD was diagnosed to a clinical dementia entity that typically presented with a progressive amnestic syndrome with the subsequent appearance of other cognitive and neuropsychiatric changes, which have been severe enough to impair activities of daily living and social function.

Current evidence suggests that the accumulation of Aβ plaque and structural, biological changes start to occur during a preclinical phase beginning as early as 10 to 20 years prior to the emergence of clinical symptoms of AD (Dubois et al. 2010; Jack et al. 2011; Sperling et al. 2011; Bateman et al. 2012). Therefore several activities to leave the concept of the full picture of dementia as a first step of diagnosis for AD have been started and AD is now considered as a continuum with a long-lasting preclinical phase without signs and symptoms of dementia or AD.

This view is supported by recent advances in CSF and imaging biomarkers of AD, which provide additional proof of diagnosis in absence of clear clinical manifestations. As the biomarkers field is evolving, in vivo information about the pathophysiology and pathogenetic processes associated with AD over time will be available.

As a consequence, populations of early and even presymptomatic patients are being included in clinical development programs. The inclusion of prodromal patients might enable treating individuals, hypothetically, at a time when some drugs may be more effective than they would be later in the illness.

These changes need consideration in a revision of the current AD guidance as e.g. assessment tools need to be more sensitive and the requirement of two co-primary endpoints addressing improvement of cognition and functional activities of daily living is not feasible in in such a patient population.

2. Problem statement

Three major issues have been important for assessment of recent and future clinical trial protocols in AD and other dementias:

1. new research diagnostic criteria are used in clinical trials for different stages of AD
2. the potential use of several biomarkers in the different stages of drug development,

3. The use of appropriate outcome measures with adequate clinical relevance to be used at any stage of the disease continuum

Recently several papers on new diagnostic criteria for AD have been published (Albert et al. 2011, Dubois et al. 2007 and 2010, McKhann et al. 2011, Sperling et al. 2011). Although full validation of these research criteria has not been finalized they are already used in ongoing clinical trials and data on their sensitivity, specificity and positive or negative predictive value are rapidly emerging.

Moreover several biomarkers including genetic markers, cerebrospinal fluid markers and brain imaging markers (MRI, PET, SPECT) have been studied extensively and are under evaluation. During the last two year experience from finalized clinical trials and large research consortia like ADNI or others have been published on potential use of biomarkers.

In terms of the new research diagnostic criteria the biomarkers can be separated into two broad categories: markers of amyloid-β (Aβ) and markers of neuronal degeneration as phosphorylated tau in CSF, imaging markers of synaptic function or imaging markers of neuronal loss and brain atrophy. Information from these biomarkers may allow recognition of patients with prodromal/predementia stages of AD.

In terms of the types of biomarkers, they can be separated according to their potential use in AD trials in: diagnostic – for determining diagnosis; enrichment – for reinforcing entry criteria; prognostic – for determining course of illness and predictive – for treatment outcomes. Biomarkers however for the most part still require validation for most of these particular purposes.

These new developments are not reflected in the current guidance of medicinal products of AD. Consequently since 2011 numerous scientific advices have been given for development programs on medicinal products for treatment of AD and CHMP has adopted and published four qualification opinions for use in the development of medicines for AD. Three of these qualification opinions are for biomarkers to help identify and select patients at the pre-dementia stage of the disease. The fourth one is for a biomarker to be used to select patients for clinical trials in mild and moderate AD. In August 2013, a public consultation ended on a qualification opinion for a novel model of disease progression and trial evaluation in mild and moderate Alzheimer's disease. The simulation tool is intended to provide a quantitative rationale for the selection of study design and inclusion criteria for the recruitment of patients.

In the diagnostic area the approval of the first radiopharmaceutical florbetapir (18F) for positron-emission-tomography (PET) imaging of beta amyloid neuritic plaques in the brain by the European Commission in January 2013 based on the recommendation of the CHMP has been another step forward. This diagnostic agent can be used, in conjunction with a clinical assessment, in patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline. Two other diagnostic radiopharmaceuticals for detection of Aß in the brain (florbetaben (18F) and flutemetamol (18F)) are currently under assessment.

All these changes need new study designs and assessment tools to monitor disease progression and to evaluate therapeutic interventions in patients with preclinical/prodromal AD.

3. Discussion (on the problem statement)

The following critical aspects should be discussed in the update of the guidance document:

- The impact of new diagnostic criteria for AD including early and even asymptomatic disease stages on clinical trial design.

- The choice of outcome parameters and need for distinct assessment tools with regard to the different disease stages in AD (different signs and symptoms, differences in change over time, severity).
- Assessment of efficacy and safety in different age groups (e.g. old versus very old).
- Potential use of biomarkers and their temporal relationship with the different phases of AD in different stages of drug development (mechanism of action, use as diagnostic test, enrichment of study populations, stratification for subgroups, safety and efficacy markers, etc.).
- Design of long term efficacy and safety studies.
- Usefulness of combination therapy and corresponding study designs.

All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account.

4. Recommendation

To take current scientific developments in the scientific community and recent experience in scientific advice and qualification procedures at EMA into consideration updating of the current guidance on medicinal products for the treatment of Alzheimer's disease is recommended by CNSWP.

5. Proposed timetable

It is anticipated that the updated draft CHMP guidance will be available within 6 months after adoption of the concept paper by CHMP.

6. Resource requirements for preparation

The preparation will involve the CNSWP. Close collaboration with the BSWP and SAWP is planned.

7. Impact assessment (anticipated)

It is aimed that the updated "Note for guidance on the development of medicinal products for the treatment of Alzheimer's disease and other dementias" will be helpful to achieve consensus in the evaluation of such products by regulatory authorities in the European Community. Furthermore, it is expected, that such guidance document would improve quality and comparability of development programs for this specific indication by pharmaceutical companies.

8. Interested parties

The interested parties in the guidance document include academia and learned societies (e.g. European College of Neuropsychopharmacology (ECNP); Alzheimer's Association; European Alzheimer's Disease Consortium (EADC); European Federation of Neurological Societies (EFNS); European Union Geriatric Medicine Society (EUGMS)), patients' organisations (e.g. Alzheimer Europe (AE); AGE Platform Europe (AGE), European Federation of Neurological Associations (EFNA)), pharmaceutical industry (e.g. EFPIA and others); The Global CEO Initiative on Alzheimer's Disease (CEOi), and regulatory agencies other than EMA.

9. References to literature, guidelines, etc.

Albert, M. S., S. T. DeKosky, et al. (2011). "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimer's & dementia : the journal of the Alzheimer's Association **7**(3): 270-279.

Ballard, C., S. Gauthier, et al. (2011). "Alzheimer's disease." Lancet **377**(9770): 1019-1031.

Broich, K., M. Weiergraber, et al. (2011). "Biomarkers in clinical trials for neurodegenerative diseases: Regulatory perspectives and requirements." Progress in Neurobiology **95**: 498-500.

Carillo, M.C., Vellas B. (2013). " New and different approaches needed for the design and execution of Alzheimer's clinical trials. Alzheimer's Dementia **9** (4): 436-437

Cortes-Blanco, A., Prieto-Yerro, C., Martinez-Lazaro, R., Zamora, J., Jiménez-Huete, A., Haberkamp, M., Pohly, J., Enzmann, H., Zinserling, J., Strassmann, V., Broich, K. (2013) Florbetapir (^{18}F) for Brain Amyloid Imaging - Highlights on the European marketing Approval. Alzheimer & Dementia, accepted for publication.

Cummings, J.L. (2011) "Alzheimer's disease clinical trials: changing the paradigm." Curr Psychiatry Rep **13**: 437-442.

Dubois, B., H. H. Feldman, et al. (2010). "Revising the definition of Alzheimer's disease: a new lexicon." Lancet Neurol **9**(11): 1118-1127.

Dubois, B., H. H. Feldman, et al. (2007). "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria." Lancet Neurol **6**(8): 734-746.

Gorelick, P.B., Scuteri, A. et al. (2011). "Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/American stroke association. Stroke **42** (9): 2672-2713.

Hampel, H., R. Frank, et al. (2010). "Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives." Nat Rev Drug Discov **9**(7): 560-574.

Hampel, H., G. Wilcock, et al. (2011). "Biomarkers for Alzheimer's disease therapeutic trials." Progress in Neurobiology **95**: 579-593

Jack, C.R, Vemuri, P. et al. (2012). "Shapes of trajectories of five major biomarkers of Alzheimer's Disease." Arch Neurol **69** (7): 856-867

Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013

Isaac, M., S. Vamvakas, et al. (2011). "Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: Cerebro-spinal-fluid related biomarkers for drugs affecting amyloid burden - Regulatory considerations by European Medicines Agency focusing in improving benefit/risk in regulatory trials." Eur Neuropsychopharmacol **21**(11): 781-788.

Kester, M.I., P.G. Scheffer, et al. (2011). "Serial CSF sampling in Alzheimer's disease: specific versus non-specific markers." Neurobiol Aging **33** (8): 1591-1598.

Klunk, W.E. (2011). " Amyloid imaging as a biomarker for cerebral ß-amyloidosis and risk prediction for Alzheimer dementia." Neurobiology of Aging **32** (Suppl. 1): S20-S36

Kozauer, N., Katz, R. (2013) Regulatory innovation and drug development for early-stage Alzheimer's disease. N Engl J Med **368** (13): 1169-1171

Landau, S.M., Lu, M. et al. (2013). „Comparing PET imaging and CSF measurements of Aß." Ann Neurol: doi: 10.1002/ana.23908. [Epub ahead of print]

Mangialasche, F., A. Solomon, et al. (2010) "Alzheimer's disease: clinical trials and drug development." Lancet Neurol **9**: 702-716

Manolis, E., S. Vamvakas, et al. (2011). "New pathway for qualification of novel methodologies in the European Medicines Agency." Proteomics Clin Appl **5**(5-6): 248-255.

McEvoy, L.K. Brewer, J.B. (2012). "Biomarkers for the clinical evaluation of the cognitively impaired elderly: amyloid is not enough." Imaging Med **4** (3): 343-357

McKhann, G. M., D. S. Knopman, et al. (2011). "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimer's & Dementia **7** (3): 263-269.

Mullane, K., Williams, M. (2013). "Alzheimer's therapeutics: continued clinical failures question the validity of the amyloid hypothesis – but what lies beyond?" Biochem Pharmacology **85**, 289-305

Querfurth, H. W. and F. M. LaFerla (2010). "Alzheimer's disease." N Engl J Med **362**(4): 329-344.

Richard, E., Schmand, B. et al. (2012)" The Alzheimer Myth and biomarker research in dementia." J Alzheimer's Dis **31**: S203-S209.

Sperling, R. A., P. S. Aisen, et al. (2011). "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimer's & dementia : the journal of the Alzheimer's Association **7**(3): 280-292.

Sperling, R.A., Johnson, K. (2013). Biomarkers of Alzheimer Disease: current and future applications to diagnostic criteria. Continuum **19** (2): 325-338.

Storandt, M., D. Head, et al. (2012). "Toward a multifactorial model of Alzheimer disease." Neurobiol Aging Epub ahead of print (Jan 17).

Vellas, B., P.S. Aisen, et al. (2011). "Prevention trials in Alzheimer's disease: an EU-US task force report." Progress in Neurobiology **95**: 594-600.

Vellas, B., Carillo, M.C., et al. (2013). "Designing drug trials for Alzheimer's disease: what we have learned from the release of the phase III antibody trials: a report from the EU/US/CTAD task force. Alzheimer' Dementia **9** (4): 438-444

Weiner, M.W., D.P. Veitch, et al. (2013) "The Alzheimer's Disease neuroimaging Initiative: a review of papers published since its inception." Alzheimer's Dementia **9** (5): e111-194

Wiesmann, M., Kiliaan, A.J., et al. (2013) „Vascular aspects of cognitive impairment and dementia." J Cereb Blood Flow Metab: doi: 10.1038/jcbfm.2013.159. [Epub ahead of print]