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Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer´s disease and other dementias

Important note to reader:

This document follows the release of the draft Concept paper announcing the need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias (EMA/CHMP/617734/2013), and the announcement of the EMA public workshop on the clinical investigation of medicines for the treatment of Alzheimer's disease to be held on 24-25 November 2014.

Acknowledging the current uncertainties regarding the pathophysiology of Alzheimer's disease, the relevance of biomarkers and the definition of the various stages of the disease, the document is intended to provide some basis for discussion ahead of the EMA workshop. The output of the workshop will be taken into account in the development of the draft revision of the guideline which will then be released for public consultation.

* This correction includes only minor editorial changes (i.e. cross-reference fixing and spell-checking in Section 4 and minor typos in Definitions and References).

Keywords	***Alzheimer disease, clinical diagnostic criteria, Alzheimer biomarkers, preclinical Alzheimer disease***

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Executive summary

Dementia is a heterogeneous class of diseases and based on etiologic factors, pattern of impairment, course of dementia and laboratory and imaging tools distinct subtypes of dementia syndromes are identifiable. Alzheimer´s disease (AD) is the most common cause of dementia, followed by vascular dementias (VaD) or mixed forms of AD and VaD. Other forms of neurodegenerative disorders (e.g. Lewy body disease, frontotemporal dementia) are accompanied with dementia as well. For regulatory purposes high specificity but also high sensitivity of diagnostic criteria will be needed.

This document takes into account recent paradigm shifts in diagnostic criteria considering AD as a disease continuum with a long-lasting presymptomatic phase which precedes 10-20 years the onset of dementia. There is now a consensus that treatment options should be evaluated in earlier disease stages before the full picture of dementia is reached. While the general approach for drug development in mild to moderate and severe Alzheimer dementia is still valid, this discussion paper aims at integrating the requirements for development programs which start earlier in the disease course including patients with preclinical and prodromal AD with the necessary adaptations to the distinct manifestations of the illness at these stages.

This document focusses on AD but other dementias are also briefly addressed. Acknowledging the current uncertainties regarding the pathophysiology of Alzheimer's disease (AD), the relevance of biomarkers and the definition of various stages of AD, this document is intended to provide some basis for discussion ahead of the EMA workshop on the clinical investigation of medicines for the treatment of Alzheimer's disease to be held on 24-25 November 2014. The output of the workshop will be taken into account in the development of the draft revision of the guideline which will then be released for public consultation.

Request of scientific advice for specific recommendations or qualification procedures concerning development programs in these disorders are strongly encouraged.

1. Introduction (background)

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, diagnostic criteria of ICD or DSM have not been used in clinical research or development programs for AD. Based on this definition AD was diagnosed as a clinical dementia entity that typically presented with a progressive amnestic syndrome with the subsequent appearance of memory and other cognitive deficits, which have been severe enough to impair activities of daily living and social function. The diagnosis was probabilistic requiring for final diagnosis histopathological confirmation (McKhann et al. 1984). Early trials in patients with mild cognitive impairment (MCI), including patients at early stages of AD, used the Mayo Clinic criteria which required a stringent definition of memory impairment and the preservation of other cognitive functions (Petersen et al. 1999).

Recently, there has been a paradigm shift in the diagnostic conceptualization of Alzheimer´s disease based on current evidence suggesting that structural and biological changes start to occur during a preclinical phase beginning decennia prior to the emergence of clinical symptoms. In 2007 the International Working Group (IWG) on research diagnostic criteria for AD provided a new framework that moved AD from a clinical-pathological to a clinical biological entity. In this concept, diagnosis is anchored to the presence of biomarkers, which provide additional proof of diagnosis in absence of clear clinical manifestations. The National Institute on Aging - Alzheimer´s Association (NIA-AA) diagnostic criteria published in 2011, similarly adopted the concept of AD as a pathophysiological continuum with

a temporal order of biomarker changes. According to NIA-AA biomarkers are supportive, however not mandatory for diagnosis (see section 4.3.2.). Both diagnostic criteria use a similar terminology to define three stages in the Alzheimer disease continuum: preclinical AD, MCI due to AD (NIA-AA) or prodromal AD (IWG) and AD dementia. Harmonization of these sets of clinical diagnostic criteria is needed and efforts are already undertaken as diagnostic criteria undergo regular update and refinement (Morris et al. 2014, Dubois et al. 2014), however, prospective clinical data are required to validate a specific diagnostic framework. The distinction of major and mild neurocognitive disorder due to AD has also been introduced in the DSM 5, in this latest revision the diagnosis remains clinical and biomarkers are not included (see Definitions). At the same time there is substantial progress in the clinical definition of non-AD dementias which helps to improve the sensitivity of the diagnostic criteria of AD by reducing the level of uncertainty. From a regulatory perspective the proposed IWG/NIA-AA criteria are accepted for diagnosis of AD for research purposes and for trial enrichment. As the biomarker field is rapidly evolving they might be translated also to clinical settings to improve diagnosis in practice in the future.

In consequence the standardization and harmonization in the use of biomarkers for different purposes needs further improvement. In parallel, the development, validation and use of reliable and sensitive instruments to measure cognition, functional, behavioural and neuropsychiatric symptoms especially in early disease stages are strongly encouraged.

We are well aware that the amyloid cascade hypothesis has significantly influenced drug development for AD in the last decades. Due to the failures of the recent amyloidocentric therapeutic approaches the validity of the amyloid cascade hypothesis has been questioned and many researchers are working now on revision/modification of it. Based on the data available today there is no proof of validity or invalidity possible, however this should be taken into consideration and development of preclinical and clinical models for proof of concept are encouraged before late stage clinical developments are planned.

2. Scope

The discussion paper aims to take these developments into account and discusses:

- 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).
- Potential use of biomarkers and their temporal relationship with the different phases of AD in different stages of drug development (mechanism of action, target engagement, use as diagnostic test, enrichment of study populations, stratification for subgroups, safety and efficacy markers, etc.).
- Design of long term efficacy (maintenance of effect) and safety studies.
- Usefulness of combination therapy and corresponding study designs.
- Stand-alone symptoms (e.g. neuropsychiatric symptoms including agitation, aggression, depression, sleep-wake cycle disturbances)

Qualification and/or validation of a certain biomarker as diagnostic tools or as a surrogate endpoint is out of the scope of this document and may be outlined in detail in separate upcoming documents after EMA qualification processes (Ref. EMA/CHMP/SAWP/72894/2008).

3. Legal basis and relevant guidelines

This document has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83/EC as amended and relevant CHMP Guidelines, among them:

- Dose-Response information to Support Drug Registration (CPMP/ICH/378/95 (ICH E4))
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96 (ICH E9))
- Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 (ICH E10))
- Points to Consider on Adjustment for Baseline covariates (CPMP/EWP/2863/99)
- Points to Consider on Missing data (CPMP/EWP/177/99)
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)
- Guideline on the choice of a Non-Inferiority Margin (CPMP/EWP/2158/99)
- Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95 (ICH E1A))
- Studies in support of special populations: geriatrics (CPMP/ICH/379/99 (ICH E7))
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.*)
- Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005)
- Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP/330418/2012 rev. 2)

Special consideration should be given to the qualification procedures as such and particularly for Alzheimer's disease:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0.

4. Specific considerations when developing products for the treatment of Alzheimer´s disease

4.1. General strategy

The strategy for demonstrating efficacy will depend on the mechanism of action/target engagement of the new product and whether it is expected to have disease modifying activity or whether the treatment effect is expected to be temporarily symptomatic with no effect on the course of the disease. The clinical development strategy also needs to consider whether the new product is intended to be used in combination with current standard treatment (i.e. cholinesterase-inhibitors, memantine), whether it is to be developed as an alternative monotherapy, or whether combination of disease modifying therapies targeting similar or different pathophysiological mechanisms are envisaged.

4.2. The main goals of treatment for dementia

- Primary prevention of symptomatic disease by intervention in suspected pathogenic mechanisms at a pre-symptomatic stage.
- Disease modification with slowing or arrest of symptom progression and evidence of delay in the underlying pathological process.

- Symptomatic improvement, which may consist in enhanced cognition, functional improvement and/or improvement in neuropsychiatric and behavioural dysfunction.
- Stand-alone symptoms as part of AD may also be studied, e.g. agitation/aggression, depression and neuropsychiatric symptoms

4.3. Patient characteristics and selection of population

4.3.1. Autosomal dominant AD

Autosomal dominant Alzheimer's disease based on several known AD-related mutations allow monitoring of the disease course and specific biomarkers over time from the early completely asymptomatic stages up to the full picture of dementia. Studies (e.g. Alzheimer's Prevention Initiative (API), Dominantly Inherited Alzheimer Network (DIAN)) are ongoing to measure pathophysiological changes over time using Cerebrospinal Fluid (CSF) biochemical markers of AD, brain amyloid deposition and brain metabolism with Positron Emission Tomography (PET), structural imaging with Magnetic resonance imaging (MRI) techniques as well as progressive cognitive and functional impairment (Reiman 2011, Bateman 2012). So patients with autosomal dominant inherited forms of AD, although representing less than 1 % of cases, serve as an important database for the development of new therapies and validation of assessment tools. From a regulatory perspective, results from trials enrolling patients with familiar AD cannot be immediately extrapolated to sporadic AD populations, however, data can be used as supporting evidence for indications in sporadic AD.

4.3.2. Sporadic AD

Approximately 99% of the AD cases are sporadic and the exact underlying causes are not yet established. Stringent diagnostic criteria with high sensitivity and specificity are needed to identify homogeneous study populations with the underlying Alzheimer pathological process. Several diagnostic criteria have been developed, which are similar but show important differences.

International Working Group Criteria (IWG criteria; Dubois et al. 2007, 2010, 2014)

According to the IWG criteria, the diagnosis of AD requires a characteristic pattern of episodic memory impairment and the presence of in vivo AD pathology, as indicated by one or more abnormal biomarkers that demonstrate either the molecular pathology of AD or the consequences of that pathology. The same requirements apply to the subcategories of prodromal AD and AD dementia, which are differentiated solely by the absence or presence, respectively, of functional impairment. Preclinical AD, by definition, lacks symptoms of memory or other cognitive impairment. It is divided in two sub-categories. To diagnose asymptomatic at risk for AD, abnormal AD biomarkers that indicate the molecular pathology of AD must be present. Presymptomatic AD is characterized by the presence of an autosomal dominant monogenic mutation for AD (see section 4.3.1. above and Definitions for details). The IWG criteria also distinguish mixed AD and atypical forms of AD with atypical clinical presentations which have to be taken into account for a careful diagnosis (see Section 5 and Definitions).

National Institute of Aging-Alzheimer's Association Criteria (NIA-AA criteria; Albert et al. 2011, Sperling et al 2011)

A model for staging preclinical AD was based on a hypothetical temporal ordering of biomarker changes which is a pre-requisite for the NIA-AA criteria. Similar to the IWG criteria three major stages in the AD continuum are distinguished. Preclinical AD refers to the pathophysiological stage when in vivo molecular biomarkers of AD are present, but clinical symptoms are absent. MCI due to AD is

defined as the symptomatic predementia phase of AD. AD dementia refers to dementia as determined by intra-individual decline of cognition and function caused by the pathophysiology of AD and encompasses the mildest to the most severe dementia stages (see Definitions). Atypical presentations are addressed with the term possible AD dementia and similarly to IWG mixed AD refers to comorbid disorders with the potential to affect cognition when at the same time diagnostic criteria for AD are fulfilled.

At this stage NIH and IWG criteria are still not fully validated and undergo constant refinement with a recent revision according to advances in the biomarker field of research as published by IWG (Dubois 2014). Both criteria have in common the recognition of a preclinical stage of the disease, the acceptance of a diagnosis of AD prior to dementia and the incorporation of AD biomarkers to diagnose (IWG) or provide support for the diagnosis (NIA-AA) of AD. The differences in terms of how AD is conceptualized, the terminology used and whether biomarkers should be incorporated in the diagnostic algorithm are recognized. It is important, that MCI due to AD according to the NIA-AA criteria and those for Prodromal AD as published by IWG show significant differences (see table in the Annex) and may lead to different study populations:

IWG: objective memory impairment and positive biomarker mandatory

NIA-AA: subjective or objective memory impairment, positive biomarker supportive but not mandatory.

It is not settled yet which criteria are the most sensitive and specific in the clinical setting. Efforts to harmonize these diagnostic criteria are under way (Morris 2014) and thus from a regulatory perspective any recommendation of diagnostic criteria particularly for early AD (i.e. prodromal AD/ MCI due to AD and preclinical AD) is still kept open.

It is important that inclusion criteria for patient selection are as homogeneous as possible in order to comprise the possibility for carrying out global development programmes. In this regard, some biomarkers have already been accepted for enrichment of study populations (see Annex 1), however, they might be reconsidered according to new research data and further use of qualification procedures is encouraged.

For both IGW and NIA/AA sets of criteria, preclinical AD is defined an asymptomatic population where the presence of AD pathology is measured by validated biomarkers. Since no biomarker is yet validated for this purpose, interventional clinical trials in this population have to be supported by a strong rationale and proof of concept.

4.4. The role and type of biomarkers

Biomarkers function as surrogates for pathophysiological lesions in AD. New proposed diagnostic criteria for AD incorporate the use of biomarkers which show either the engagement to target by assessing amyloid β in the brain or CSF, or synaptic or neuronal damage as indicated in reduced glucose metabolism, grey matter atrophy or tau in CSF (Villemagne 2013). Information from these biomarkers may allow enrichment of patient populations with “prodromal/MCI due to AD” stages of AD. While the core clinical criteria remain the main landmark of the diagnosis of AD in clinical practice, biomarkers may increase the specificity of the diagnosis (de Souza 2014).

In terms of the types of biomarkers, they can be theoretically 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 and safety assessment.

Biomarkers however for the most part still require validation for many of these particular purposes since standardization (e.g. cut-off values, assay variability) and operationalization have not yet been completed (Morris 2011). However, cerebrospinal fluid markers as well as MRI and PET imaging markers are accepted for the enrichment of study populations (see Qualification advices in Annex 1).

Recently in the diagnostic area the approval of the radiopharmaceuticals florbetapir (18F), (florbetaben (18F) and flutemetamol (18F) for positron-emission-tomography (PET) imaging of beta amyloid neuritic plaques in the brain by the European Commission based on the recommendation of the CHMP have been another step forward. Despite some caveats this diagnostic agent can be used (only in conjunction with a proper clinical assessment) in patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline. For the time being it's not clear whether CSF and PET amyloid biomarkers are interchangeable and it is strongly advised to measure not only Aβ1-42 but also T-Tau or P-Tau levels (Medina et al. 2014). Downstream topographical markers of brain regional structural and metabolic changes (e.g. hippocampal atrophy assessed by MRI, cortical hypometabolism by FDG PET) while having insufficient pathological specificity may be particularly valuable for detection and quantification of disease progression. Many activities are underway on new biomarkers that may emerge in the future, e.g. PET imaging with markers for Tau or neuroinflammation or markers as visinin-like protein-1 and sAPPß (Cavedo et al. 2014; Mapstone et al. 2014; Fiandaca et al. 2014).

4.5. Assessment of therapeutic efficacy

Different requirements to assess therapeutic efficacy are distinguished according to the stage of the disease (preclinical, prodromal, mild, moderate or severe dementia) and the potential claims of treatment, e.g. symptomatic improvement or disease modification and primary prevention (see section 4.2). A longitudinal model for describing changes in cognition in patients with mild and moderate AD, and for use in assisting in trial designs in mild and moderate AD has been qualified (see Annex 1).

4.5.1. Symptomatic improvement

Generally, a co-primary endpoint approach is required to ensure the clinical meaningfulness of a cognitive and functional benefit that may be observed.

In advanced stages of dementia beside the cognitive deficiencies functional impairments are more pronounced and stabilization or improvement in ADL may be more important endpoints. Behavioural problems with agitation and aggression do occur with major impact on patients and carers. Not many studies have been performed in patients with severe dementia, so there is a need for adaptation of assessment tools, which allow a comprehensive evaluation of the functional and global domains with special emphasis on ADL and behavioural abnormalities. Study adherence may also be an issue in this population.

It is recognized that in earlier disease stages 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 (ADL) would be difficult to establish in such a patient population. However, also in this case the clinical relevance of the results should be demonstrated. In preclinical patients symptomatic improvements are not a reasonable outcome assessment due to the lack of symptoms.

4.5.1.1 Criteria of efficacy

i) Dementia stage of AD

Improvement of symptoms should be assessed in the following three domains:

1) cognition, as measured by objective tests (cognitive endpoint);

2) (instrumental) activities of daily living (functional endpoint).

3) overall clinical response, as reflected by global assessment (global endpoint).

Efficacy variables should be specified for each of the three domains. Two primary endpoints should be stipulated reflecting the cognitive and the functional or global domain in mild to moderate AD. Functional domain is prioritized over global domain as co-primary endpoint and global assessment should be evaluated as a secondary endpoint. The study should be designed to show statistical significant differences in each of the two primary variables. If this is achieved, then an assessment should be made of the overall benefit (response) in individual patients, and the effect of treatment should be illustrated in terms of the proportion of patients who achieve a clinically meaningful benefit (response) defined based on consideration of the natural progression of disease, e.g. for a claim of short term treatment, responders may be defined at 6 months as improved to a relevant pre-specified degree in the cognitive endpoint and at least not worsened in the two other domains.

Secondary endpoints of interest may include neuropsychiatric and behavioural symptoms. For a claim in these symptoms, the trial should be designed accordingly and neuropsychiatric and behavioural symptoms should be measured using specific and validated scales, as part of the confirmatory testing strategy. It is recommended to address these additional hypotheses through a separate dedicated trial (see Stand-alone symptoms below).

In the more advanced forms of the disease, i.e. severe dementia, changes in cognitive performance may be less relevant to quantify. Hence choice of functional and global domains as primary endpoints may be more appropriate to establish clinically relevant symptomatic improvement in this severely impaired population.

Measurement tools (cognitive, functional or global) should be externally validated, pertinent in terms of realistically reflecting symptomatic severity, sufficiently sensitive to detect modest changes related to treatment, reliable (inter-rater; test/retest reliability) and as far as possible easy to use and of short duration, allowing the possibility of easy combination with other tests. They should be calibrated in relation to subpopulations of different social, educational and cultural backgrounds in order to have validated norms available for the interpretation of the results. They should be standardised for use in different languages and cultures. The frequency of testing and the number of equivalent versions of some tools (e.g. highly specific memory tests) should be justified to ensure that the learning effect with repeated administration is minimal.

Applicants may need to use several instruments to assess efficacy of putative drugs for treatment of dementing conditions because:

a) there is no ideal measurement instrument at the present time. Whilst a large number of methods for evaluation of cognitive functions and behavioural changes have been suggested, none has convincingly emerged as the reference technique, satisfying the above set of requirements, particularly taking into consideration prodromal/MCI patient populations. Hence the choice of assessment tools should remain open, provided that the rationale for their use is presented and justified

b) demented patients are poor observers and reporters of their own symptoms and self-report scales of behaviour tend therefore to be less sensitive to treatment effects than observer-related instruments, particularly in moderate to severe disease stages. Caregiver evaluations should therefore be part of the assessment, even though the risk of bias should not be underestimated in these advanced disease stages.

It is recommended that each domain is assessed by a different rater who should be blinded to treatment allocation. If side effects exist which can unblind the investigator, all outcome raters should be denied access to this information as far as possible. In advance, and if necessary, the raters should be trained so that variability is minimised and inter-rater reliability is maximised with the assessment tools used.

Adjunctive symptomatic effect

If a claim in symptomatic effect as adjunctive therapy to currently approved drugs (AchEis) is pursued, improvement of symptoms should be assessed in two of the following domains: 1) cognition, as measured by objective tests (cognitive endpoint); 2) (instrumental) activities of daily living (functional endpoint) or overall clinical response, as reflected by global assessment (global endpoint). The co-primary endpoint approach is preferred, however, in patients at a moderate to severe stage of the disease, an additional effect on either the functional or global domain without worsening in cognition may be accepted, provided that it proves to be clinically meaningful.

ii) Prodromal AD/MCI due to AD

In principle, the dual outcome approach is still required but maybe in practice not feasible the milder the symptoms are, due to the lack of sensitive assessment tools. As functional impairment is usually not measurable in prodromal/MCI patients, its use as co-primary endpoint in this early stage of the disease is not mandatory. However, patients with mild neurocognitive impairment due to AD (DSM-5), prodromal AD (IWG) or MCI due to AD (NIA-AA) who are closer to the onset of dementia are supposed to have subtle but already noticeable impairments in their daily functioning. Assessment tools for cognition and function or global impairment used in mild to moderate dementia need to be validated for these early stages or more sensitive new tools need to be developed. The applicant will be required to justify the instruments selected with respect to their psychometric properties and the population studied. The use of composite scales validated in early stage patients to assess both cognition and function as a single primary outcome measure is also considered appropriate. The studies should be designed to show statistical significant differences versus baseline. It is important to demonstrate that any treatment effect is not entirely driven by cognition or function alone. The clinical Dementia Rating Scale, specifically the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score, the recently introduced ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC) or Alzheimer's prevention initiative composite cognitive test score (Langbaum et al. 2014) might be examples of suitable tools (see 4.5.3). However, the clinically meaningful change (e.g. minimal relevant difference, definition of responders) still needs to be established and there are issues with cross-cultural applicability.

iii) Stand-alone symptoms (e.g. neuropsychiatric symptoms including agitation, aggression, depression)

In general symptomatic treatment of AD includes also treatment of neuropsychiatric symptoms like agitation, aggressive behaviour, apathy, psychosis or depressive symptoms. In order to be considered as a stand-alone indication it is expected that the mechanism of action of the medicinal product would be relevant and specific for the treated neuropsychiatric symptoms. This requires reliable and valid measurement tools for the studied patient population in the specific stages of the disease; symptoms in early stages will be different from the later stages of disease and issues of “pseudospecificity” should be considered.

It is recommended to address such stand-alone indications in separate dedicated trials; study duration depends on the symptoms to be studied and should be justified. Cognition and function should be measured in these trials as secondary endpoints in order to exclude a deteriorating effect on these domains.

4.5.1.2 Design features

i) Dementia stage of AD

It is acknowledged that the feasibility of long term placebo controlled studies has become seriously limited due to the availability of several symptomatic treatments. However, since substantial differences between placebo patients in the different dementia trials have been shown and improvement without treatment cannot be ruled out the preferred design option is still a three-arm study comparing the test product to an already approved treatment and to placebo for assay sensitivity. The active control is needed in order to place the new treatment in the context of other available treatment options. In order to minimize the ethical concerns for the use of placebo, a placebo controlled trial, while people are on standard therapy, or not, can be considered. Stratification according to baseline therapy should be undertaken. Such a study most likely will have influences on the label claim. Alternatively a superiority trial versus active control could be considered. Due to concerns over assay sensitivity, the use of a non-inferiority design versus active control only will not be accepted as proof of efficacy.

Study duration will be highly dependent of the studied patient population and the intention of treatment. In patients with mild to moderate AD a placebo controlled study duration of 6 months might be sufficient to demonstrate symptomatic improvement.

On-treatment follow-up of at least 12 months is recommended for demonstrating long term safety. This can be achieved with an extension of the trial over the initially scheduled period in patients considered as responders and/or asking for continuing the treatment. In addition to responding adequately to an ethical issue, this allows to accumulate data on medium/long term safety of the drug.

Evaluation of efficacy and safety should be performed at regular intervals, depending on the anticipated rapidity of action of the medicinal product and the duration of the trial. After the end of the treatment, the state of the patients should be followed for possible adverse events related to withdrawal treatment for a period appropriate for the drug being tested.

ii) Prodromal AD / MCI due to AD

For prodromal AD, no products are approved, so placebo is the comparator of choice. In this population, 6 months may not be sufficient to capture symptom changes and much longer study durations might be necessary to assess therapeutic efficacy even for a symptomatic treatment. Assessment of efficacy and safety at regular intervals is especially important (see above). In the prodromal AD/MCI due to AD population it is even more important to collect data on maintenance of therapeutic effect after the double blind phase; for this purpose a parallel arm extension or a randomized withdrawal trial are recommended.

4.5.2. Disease modifying effects

4.5.2.1 Criteria of efficacy

i) Dementia and prodromal AD / MCI due to AD

From a regulatory point of view, a medicinal product can be considered as disease modifying, if the progression of the disease as measured by assessment tools addressing both cognition an function is reduced or slowed down (see section Tools for outcome assessment) and if these results are linked to a significant effect on adequately qualified and validated biomarkers.

At the time of finalisation of this document no clinical trial has led to a successful claim of disease modification in AD. For regulatory purposes, 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 in the rate of decline of clinical signs and symptoms (change in slopes). However, a pharmacologically reversible effect that increases over time could also lead to such an outcome. Consequently, a true disease modifying effect cannot be established conclusively based on clinical outcome data alone. Such a clinical effect must be supported by biological evidence of a change in the pathophysiology from a biomarker programme.

In order to give a regulatory framework for the numerous variables introduced in recent clinical trials, we propose a two-step approach. If in a first step an improvement in the rate of decline of clinical sign and symptoms can be established, this may be acceptable for a limited claim (e.g. delay of disability) if efficacy in cognition and function is demonstrated. This might be more difficult to demonstrate in prodromal/MCI patients the earlier they are in the spectrum of the disease. Specific cognitive tests (isolated memory impairment) are needed for the detection and monitoring of the earliest very subtle signs of cognitive impairment and are currently under development; validation for such tools is ongoing in several studies (e.g. Donohue et al. 2014). Depending on the results these isolated cognitive measures could be used as primary outcome measure in biomarker enriched patient populations. If these results are supported by a convincing package of biological and/or neuroimaging data, e.g. showing in addition to an effect on the underlying mechanism of action a delay in the progression of brain neurodegeneration, a full claim for disease modification could be considered. Effects limited on cognition and function in the absence of any biomarker evidence merits a claim in symptomatic treatment only so absence of reversibility in randomized withdrawal studies is not sufficient.
Trial duration for such trials has to be long enough to detect a clear treatment effect; this will depend on the disease stage (see section 4.5.2.2.i below).

ii) Prevention trials

The overall goal of primary prevention in dementia is to reduce the incidence of the disease. This will be accomplished by promoting the initiation and maintenance of good health or by removing potential causes of disease in individuals without dementia or individuals with potentially modifiable (e.g. hypertension, high cholesterol) or unmodifiable (APOE4 status, high age) risk factors for dementia. Cognitive endpoints used in primary prevention trials have been the diagnosis of dementia (based on cut-off scores), significant cognitive decline and change in cognitive function based on longitudinal performance on certain tests. Unfortunately trials so far have not given conclusive results, however, this may be due to methodological reasons, e.g. high baseline variability and heterogeneous populations, ceiling effects of assessment tools, rarity of proposed outcome, etc. Therefore, in future prevention trials baseline populations, length of follow-up, timing in relation to possible dementia onset, use of valid outcomes, which are sensitive to change, etc. must be considered and should be justified.

4.5.2.2 Design features

i) Prodromal AD/MCI due to AD and mild to moderate dementia

Placebo-controlled trials are mandatory as there are no disease-modifying products approved. Since in many countries symptomatic treatment of dementia with cholinesterase-inhibitors or memantine is considered as standard of care, particularly in mild to moderate Alzheimer's disease, stratification for the use of these medications should be undertaken.

An improvement in the rate of decline of clinical signs and symptoms must be shown over a time period that is relevant to the proposed claim. Clinical outcomes in both study arms should be measured at regular intervals to establish a clinically relevant effect. The minimum duration of confirmatory trials depends on the expected progression rate and the assumed activity of the experimental compound, e.g. in patients with mild to moderate Alzheimer's disease, duration of 18 months has been assumed to be sufficient in some trials, in prodromal disease stages even longer studies might be necessary (e.g. 24 months).

So in a first approximation a hypothesis of disease modification seems most consistent with a statistical comparison of rates of change in clinical symptoms over time (slope analysis). However, it should be taken into consideration that although it is known that the natural course of disease may be approximated with a linear model over time, it is yet unclear, whether a linearity assumption holds true in the situation of a clinical trial with an intervening (potentially disease modifying) treatment effect and whether the effect of treatment is constant over the treatment course. Moreover, a comparison of the rate of change in key clinical efficacy parameters based on slope analysis between active treatment and placebo using a standard parallel design does not solve the problem that a pharmacologically reversible effect that increases over time could also lead to such an outcome (see also section 4.5.2.1.i above). The specification of the statistical model for the slope analysis is, therefore, not always straightforward. Furthermore, treatment effects might be different over the various disease stages (prodromal/MCI, mild, moderate, severe) and many of the newer or commonly used outcome measures show a non-linear change, when used for time periods longer than one year.

In consequence a delay of progression over time in the pre-specified endpoints should be established at (at least) two distinct time points in a parallel group design. Such a study can be enhanced with a phase of a randomized delayed-start or randomized withdrawal design. The magnitude of the treatment effect in terms of established outcomes, e.g. ADAS-Cog and ADL, is estimated based on the difference between placebo and experimental compound and should be linked to a significant effect on adequately qualified and validated biomarkers as secondary outcome parameters. Alternatively, the possible disease modifying effect may be addressed by a simple slope analysis supported by a time to event approach. A time to event approach is more reasonable in earlier disease stages since symptoms will be minimal and changes over time might be difficult to assess.

Both approaches to establish a disease modifying effect have their drawbacks and may be further hampered by possible improvements in placebo treated patients, differences in drop-out rates and missing data in general, poor adherence to treatment, change of treatment response with course of disease, etc. Therefore the choice of primary analysis, specification of the statistical model and the fulfilment of underlying assumptions and requirements should be justified in detail in the study protocol. Independently from the study design chosen it may be difficult to differentiate unambiguously between symptomatic and disease modifying effects only on the clinical endpoints, therefore a full claim of "disease modification" can be supported by evidence from suitable study design, accepted novel analyses, and an adequately qualified and validated biomarker, which is able to indicate an effect on the underlying pathophysiology of the dementia syndrome. Such a biomarker should reflect key aspects of the underlying disease process based on a plausible disease model.

ii) Prevention trials

Prevention trials are based on the assumption that preclinical patients who are not yet cognitively impaired, can be treated with multidomain interventions, or known safe drugs or new pharmacological targets. Efficacy is demonstrated using time to onset of cognitive impairment or time to onset of dementia as endpoints. Prevention trials require large samples and long follow up, typically of at least

5 years. Due to lack of studies no firm recommendation can be made and therefore scientific advice is recommended in case this is pursued.

iii) Combination treatment

If two disease-modifying drugs are studied concomitantly there is usually as in combination symptomatic treatments a requirement to show the contribution of each drug to the targeted mechanisms of action. In addition, the contribution to clinical efficacy has to be shown separately for each drug, usually in a trial where the combination is compared to the two monotherapy arms. However, it is acknowledged that a full factorial design may be difficult for disease modifying therapies due to the large sample sizes required in each arm over long study periods. The exclusion of monotherapy arms needs to be thoroughly justified either by the lack of efficacy in previous monotherapy programs or convincing phase 2 data demonstrating additive/synergistic effects of the combination over each monotherapy arm not only on biomarkers but also on clinical outcome parameters.

4.5.3. Tools for outcome assessment

- **Objective cognitive tests**

The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), dealing with memory, language, construction and praxis orientation, is widely used and can be considered as standard in trials on patients with mild to moderate Alzheimer's disease. However, due to ceiling and floor effects, its sensitivity to change is limited in early and late stages of the disease. By means of adding additional items to the original ADAS-Classic its responsiveness in patients with milder cognitive impairment is increased (Skinner et al 2012). Nevertheless, there is a need for the development of new instruments to address these limitations. For the new instruments, data are needed to provide empirical support for the construct validity and reliability of the new measurement tools (e.g. test-retest, inter-rater, internal consistency, etc). Moreover, for correct interpretation of the described results validation of these tests in normal controls and different disease states including influences by age, gender, level of education, time interval of testing etc. is necessary. Otherwise the clinical meaningfulness is not assessable.

Alternatives to the ADAS like the "Neuropsychological Test Battery for Use in Alzheimer's Disease" (NTB), the CDR-SB, the recently proposed ADCS-PACC or others have been validated and may be used.

The CDR-SB is a clinician´s interview-based global severity scale that encompasses the sum of the scores of six items measuring cognition and function. Items 1-3, provide a comprehensive and clinically relevant assessment of cognition and its impact on the patient's everyday life. Items 4-6 describe the patient's self-sufficiency outside home, his interest in hobbies and his independence in personal care activities. The CDR-SB was initially used as a staging tool for AD but has recently been validated as a longitudinal assessment of clinical function (Cedarbaum et al. 2012, Coley et al. 2011) in AD reflecting changes in both, cognition as well as function, mainly in the very mild or prodromal impairment range. The CDR-SB scoring requires extensive training and is subject to variability among ethnicity and languages.

The Alzheimer's Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC), is a cognitive composite that is weighted towards episodic memory, but also includes a timed executive function test and a global cognitive measure (MMSE) (Donohue et al 2014). The clinical relevance, the functional and long-term consequences of the subtle cognitive changes measured by ADCS-PACC in earlier disease stages is currently unknown.

If other scales than ADAS-cog are used as primary outcome measure, estimations with the ADAS-cog as secondary endpoint should supplement the results for consistency of interpretation.

- **Self-care and activities of daily living**

Usually in prodromal/MCI due to AD patients functional impairment is not clearly evident, so measurement won´t be feasible. However, in patients with later prodromal stages closer to overt dementia and with mild AD subtle impairments of function are measurable and in these populations assessment of activities of daily living (ADL) and instrumental activities of daily living (IADL) is useful to evaluate the impact of a medicinal product-related improvement in everyday functioning. Self-ratings might be applicable in these milder disease stages; however, in advanced disease stages these measurements rely largely upon the reports of relatives or carers in close and regular contact with the patient, some items of measurement are gender- and culture-biased.

Several scales have been proposed to measure either basic activities of daily living (or self-care) which relate to physical activities, such as toileting, mobility, dressing and bathing (ADL) or instrumental activities of daily living, such as shopping, cooking, doing laundry, handling finances, using transportation, driving and phoning (IADL). However, this concentration on common self-care or domestic activities disregards many activities, which in recent times may be more appropriate, e.g. use of technology. This results in low sensitivity to change of most of the used assessment scales today.

Separate measurement tools of ADL/IADL for early and advanced disease stages are needed, which add new dimensions to the existing assessment tools to allow better evaluation of a clinically meaningful change, e.g. in epidemiological studies impairments in four IADL items (handling medications, transportation, finances and telephone use) have been shown as most sensitive indicators of early stages of dementia (particularly when performance speed is taken into consideration) whereas in advanced disease stages basic ADL as toileting, dressing and bathing are sensitive indicators of change. One of the major issues for use in clinical trials is non-linearity of these changes over time due to adaptation and coping strategies of the individual patient. However, in newer studies using the “Disability Assessment in Dementia” (DAD) or the “Alzheimer Disease Cooperative Study ADL scale” (ADCS-ADL) some initial results showed linearity in change over one year in mild to moderate AD.

As many instruments are under further evaluation choice of the instrument for assessment and its applicability for early or advanced disease stages should be justified in the study protocol.

- **Global Assessment of Change**

Global assessment refers to an overall subjective independent rating of the patient’s condition by a clinician experienced in the management of patients with dementia. Despite certain limitations, the clinician's global assessment can serve as a useful measure of the clinical relevance of a medicinal product's anti-dementia effect. Moreover, global assessment, being in general more unspecified, allows detection whatever changes occur within treatment.

A global scale allows a single subjective integrative judgement by the clinician on the patient's symptoms and performance, as opposed to assessing various functions by means of a composite scale or a set of tests (comprehensive assessment). The Clinician's Interview Based Impression of Change plus (CIBIC-plus) allows assessment of the global clinical status of the demented patient relative to baseline, based on information from a semi-structured interview with the patient and the carer, without consideration of any cognitive performance from any source. The Alzheimer’s Disease Cooperative Study Unit Clinician’s Global Impression of Change (ADCS-CGIC) is another semi-structured interview based global measure incorporating information from both patient and carer. Compared to the CIBIC-plus it is more specified with focus on 15 areas including cognition, behaviour and social and daily functioning. Although such a global assessment of patients benefit is less reliable

than objective measurements of response and often appears insufficient to demonstrate by itself an improvement, it should be part of clinical trials in dementia as it represents a way to validate results obtained in comprehensive scales or objective tests, particularly when it is applied by an independent rater. The CIBIC-plus has been shown to be less responsive to drug effects than psychometric tests alone in some studies with anti-dementia drugs in AD, however, clinical global impression was more sensitive than standard measures of cognition and behaviour in a study in patients with PDD.

Contrary to global measurement of change, comprehensive assessment is meant to measure and rate together in an additive way several domains of the illness, e.g. cognitive deficits, language deficits, changes in affect and impulse control. Scores proven to be useful in describing the overall clinical condition should be used, such as the Clinical Dementia Rating (CDR).

However, rather than composite scores derived from summing or averaging scores in different domains, the use of a set of instruments to quantify individually the dimensions of impairment, disability and handicap (social participation) is encouraged by regulatory bodies.

- **Health related quality of life**

Although quality of life is an important dimension of the consequences of diseases, the lack of sufficient validation of its assessment in the different stages of AD does yet not allow specific recommendations to be made for regulatory acceptance. Further studies are required to validate adequate instruments for assessment of these dimensions in patients and their caregivers. In theory, both generic and disease specific questionnaires may be used in patients with dementia. However, in practice, it is very important to choose a questionnaire which addresses the key domains of the disease and is sensitive to reflect clinically meaningful changes. Depending on the disease stage information regarding quality of life can be obtained by the patient, by family members or professional caregivers. Based on the different perspectives of the respondent - patient or carer - the information may be divergent and sometimes even contradictory. This has to be taken into consideration in the process of validation of semi- or structured interviews and assessment scales before claims about improvement in quality of life can be achieved. The issue is further complicated by “response shift”. This term reflects on the change in the internal standards of the respondent: based on psychological, social and cultural background and resources coping processes will be facilitated, which may lead to an improvement in quality of life independent from treatment with medicinal products for dementia. These effects are clearly different in early and advanced stages of the dementing condition and must be taken into consideration.

Examples for disease specific quality of life measures are the Alzheimer’s Disease-Related QOL(ADRQL) and the QOL-Alzheimer’s Disease (QOL-AD), both show sufficient psychometricproperties and studies are ongoing to establish their sensitivity to change.

- **Behavioural Signs and Symptoms**

Although the formal clinical diagnostic criteria do not include behavioural signs and symptoms, they are an important cause of clinical deterioration in patients with more advanced stages of dementia and are associated with increased burden of disease and stress particularly for family members or caregivers. The overall frequency and severity of behavioural abnormalities increase in the later and more severe stages of dementia. Among the most frequent and disturbing behavioural symptoms are apathy, agitation, aggression and delusions. However, individual behavioural symptoms have been described as highly variable and heterogeneous in presentation, transient, recurrent or persistent in course and fluctuating in prevalence and severity.

Several assessment tools like the Behavioural Pathology in Alzheimer’s disease Rating Scale (BEHAVE-AD), the Behavioural Rating Scale for Dementia (BRSD), the Neuropsychiatric Inventory (NPI) and

others have been used as outcome measures in clinical trials. Newer tools are under development reflecting the different characteristic signs and symptoms in accordance with different disease stages.

4.6. Early pharmacology and pharmacokinetic studies

In the early phases of the development of anti-dementia medicinal products it is important to establish the pharmacological mechanism on which the drug may be thought to be effective. The supposed mode of action (i.e. symptomatic or disease modifying effect) will influence the study program. Side effects and possible surrogate markers of pharmacological activity in volunteers, if available and relevant, might give some estimation of the appropriate dose range.

Standard pharmacokinetic studies (see guideline on pharmacokinetic studies in man) must aim at defining the absorption, distribution, metabolism and elimination of the drug. Population Pharmacokinetics (popPK) models may be useful in simulation of drug concentrations in this mostly older population.

Pharmacokinetic interactions between the test drug, other anti-dementia drugs and other medicinal products, expected to be given concurrently in clinical practice, should be studied, unless clear mechanistic based evidence is available that no interaction could be expected. Reference is made to the drug interaction guideline.

As polypharmacy will be an important issue in this population, pharmacodynamic interactions between the test drug and other medicinal products (including psychoactive, antiplatelet and lipid metabolism agents), expected to be given concurrently with the test drug in clinical practice, should be studied.

If relevant, pharmacokinetic studies of the test-drug in patients with hepatic and /or renal impairment should be performed. The specific characteristics of the mostly older patients have to be taken into account with possible higher sensitivity to the pharmacodynamics of certain medicinal products.

4.7. Exploratory trials

As a successful treatment for AD may require intervention prior to the emergence of symptoms, newer development programs are now strongly focusing on earlier disease stages. Many studies have shown only minimal improvement in advanced disease stages of AD (moderate and severe). The inclusion of the same type of patients in Phases II and III is advised, as safety issues may not be the same in different subgroups. Ideally such studies are carried out in the patient's everyday surroundings. These studies in well-characterized samples of patients have the following objectives:

• preliminary evaluation of efficacy

• assessment of short-term adverse reactions from a clinical and laboratory standpoint

• determination of pharmacokinetic characteristics

• definition of doses presumed to be effective

• determination of maximal tolerated doses

The duration of such trials will depend either upon the time to measurable response that is expected, or may be one of the parameters to be assessed. The value and qualification of several biomarkers has been improved considerably and some of them may be used as primary endpoint in proof of mechanism/principle studies or as secondary endpoints in pivotal clinical trials of a disease modifying substance.

4.8. Statistical considerations

The handling of missing data, particularly resulting from early withdrawals, is of particular concern in Alzheimer's disease trials, as the proportion of patients with missing data is high and there is no clearly optimal method for handling it. Also, several approaches that are standard in other conditions perform extremely badly here. If feasible, patients withdrawn from treatment should be followed-up to capture the key endpoints and an analysis based on these data could be conducted.

Methods such as last observation carried forward (LOCF) and baseline observation carried forward (BOCF) are inappropriate, as because the condition generally declines over time, using these approaches means that patients who withdraw early are generally attributed with better values than would be achieved if they had continued, biasing comparisons in favour of treatments with more and/or earlier withdrawals.

The mixed model for repeated measures (MMRM) approach also exhibits some disadvantages, the major concern relating to the targeted estimand, since it assesses the treatment effect if the treatment is taken as directed by all patients and the blurring effect of treatment non-compliance and withdrawal is ignored. The MMRM model tends to be less robust against a decreasing treatment effect difference after treatment discontinuation, which is one reason why in CNS indications the MMRM model often yields effect estimates close to those in the subgroup of patients who complete the study as planned. Therefore it is difficult to endorse the choice of the MMRM model as the primary analysis model because of this concern that the results would tend to overestimate the true treatment effect.

Slope based analyses are similarly concerning in the presence of early withdrawals, as they assume the same slope after discontinuation as before.

Alternative choices of primary analysis method are encouraged. Possibilities include responder analyses which treat any treatment discontinuation as a non-response, or non-parametric rank analyses which rank first according to the time of drop-out and then by the measured score at the time of drop-out (or planned end of study). Rank and responder analyses do not allow for a simple interpretation of the clinical relevance of the treatment effect size on the original scale, however they are easy to apply methods to establish the existence of a statistically significant effect, and additional analyses could then be used to estimate the size of the benefit.

Methods using placebo data to impute missing values in the active arm could be useful, as could tipping point analyses which explore how bad the results for patients with missing data would have to be before a positive result it lost. Whatever choice is made must be prespecified and fully justified in the protocol.

The primary analysis will also have to be accompanied by several sensitivity analyses, not all of which should be based on the same assumptions. These could include the MMRM analysis and slope based analyses. LOCF and BOCF are not considered useful even as sensitivity analyses.

5. Other Dementias

Although specific recommendations for other types of dementias are beyond the scope of this document the same principles for symptomatic and disease modifying treatment approaches as for AD apply. Other dementias and dementia syndromes thus are only briefly addressed below. Depending on the disease stage validated clinical and biomarker instruments should be used as endpoints. In the following paragraphs some principle characteristics of the most common other dementias are briefly summarized. However, for more detailed recommendations scientific advice is recommended.

Mixed Dementia and Mixed AD

A large proportion of patients with dementia show evidence of multiple overlapping neuropathological processes. Mixed AD has been reported to represent at least 50% of all AD cases at autopsy and according to IWG has to be distinguished from atypical AD with atypical clinical presentations such as posterior variant, logopenic variant of primary progressive aphasia and frontal variant.

Very often AD and Vascular Dementia (VaD) coexist with combination of neurodegenerative and vascular changes but also other pathologies might contribute to cognitive decline in patients with mixed dementia (MIXD), e.g. normal pressure hydrocephalus, hippocampal sclerosis and other dementias such as Lewy body dementias, fronto-temporal dementia and Huntington disease.

The IWG criteria similarly to NIA-AA propose that for mixed AD diagnosis there must be evidence of typical or atypical AD based on clinical phenotype with at least one concurrent in-vivo evidence of Alzheimer´s pathology. Additionally, clinical as well as neuroimaging or biochemical evidence of the co-existing disorder should be present.

Generally, it is recommended to start the development program in the “pure” disease forms and only thereafter extend the scope of development to the mixed forms.

Vascular Dementia

In clinical trials vascular dementia has traditionally been diagnosed by the Hachinski Score and its modified versions or the criteria of the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN). Similarly to the NINCDS-ADRDA criteria for AD the NINDS-AIREN criteria allow to distinguish between possible and probable disease, they show high specificity but low sensitivity for vascular dementia. Some trials on vascular dementia also used the criteria from the State of California Alzheimer’s Disease Diagnostic and Treatment Centres (ADDTC) as inclusion criteria, that show high sensitivity but lower specificity. Independent of the criteria used for VaD inter-rater reliability is usually lower than in AD. Thus it is hardly surprising that in comparative studies different patient populations have been identified by the use of different criteria. Therefore, for regulatory purposes the NINDS-AIREN criteria with their high specificity are still preferred until better criteria become available. Longer efficacy studies of at least 12 months for symptomatic treatments might be needed since changes of symptoms over time evolve more slowly.

Lewy body dementias

Based on recent research Parkinson´s disease dementia (PDD) and dementia with Lewy bodies (DLB) are subsumed under the umbrella term Lewy body dementias, (LBD). Lewy body dementia is considered to be the second most frequent type of neurodegenerative dementia after Alzheimer´s disease. However, based on the differing temporal sequence of key symptoms and clinical features in PDD and DLB a distinction of these concise subtypes is still considered justified.

Patients with Parkinson’s disease show an increased risk for dementia based on epidemiological studies. The prevalence of dementia in Parkinson’s disease is between 24 and 50 % and 3 to 4 % of the total dementia burden is due to Parkinson’s disease. Operationalised criteria for patients with PDD have been proposed recently, however data on sensitivity and specificity have not been fully established. A current pragmatic approach requires at least one year of major parkinsonian motor symptoms before the onset of dementia symptoms appears.

In dementia with Lewy Bodies (DLB), the criteria by McKeith et al. (2005) have become a standard for studies that show a very high specificity but low sensitivity; besides the presence of dementia, clinical core features of DLB consist of rapid fluctuations in attention and concentration, recurrent visual

hallucinations and spontaneous and fluctuating features of parkinsonism. Recently, low dopamine transporter uptake has been incorporated into the revised diagnostic criteria as additional suggestive parameter.

Fronto-temporal Dementia

Fronto-temporal dementia (FTD) is considered as common cause of dementia in people under the age of 65. It is a clinically and pathologically heterogeneous disease (Chare et al. 2014). The recent International consensus papers recognise four main clinical variants - a behavioural variant (bvFTD) characterised by prominent early personality or behavioural changes (Raskovsky et al. 2011) and three primary progressive aphasia (PPA) syndromes (Gorno-Tempini et al. 2011): a non-fluent/agrammatic variant or nfv-PPA (previously known as progressive non-fluent aphasia), a semantic variant or sv-PPA (previously known as semantic dementia) and a logopenic variant or lv-PPA. The latter syndrome is distinguished by impairment of lexical retrieval and sentence repetition.

The revised criteria for behavioural variant frontotemporal dementia (bvFTD) improved diagnostic accuracy compared with previously established criteria (Neary et al 1998, McKhann et al 2001). They are structured as a diagnostic hierarchy in possible, probable and definite FTD, the latter requiring histopathological confirmation. Three major pathological subtypes of frontotemporal lobar degeneration are distinguished (FTLD-tau, FTLD-TDP or FTLD-FUS) (Mackenzie et al. 2010). Currently, no validated biomarkers are available that allow one to positively demonstrate the presence of the underlying hall mark lesions in vivo and to discriminate between the etiological subtypes. A proportion of clinically diagnosed FTD patients have underlying AD pathology and careful evaluation is required especially in patients presenting with the logopenic variant (lv-PPA).

Huntington´s disease

Other rare conditions associated with dementia such as Huntington's Disease can be diagnosed by detection of their genetic abnormality, e.g. "Huntingtin" can be reliably measured by a blood test, which allows confirmation or exclusion of Huntington's disease with great accuracy.

6. Studies in special populations

Depending on the diagnostic entity studied different age groups might be necessary, e.g. old versus very old patients with AD. A reasonable number of elderly patients (>65 years, >75 and > 85 years, respectively) should be included in the therapeutic confirmatory studies. The number of subjects 75 years and older included in (pivotal) trials should be sufficient to assess both efficacy and safety in this group.

7. Safety evaluations

In general the content of ICH E1 should be taken into consideration.
Identified adverse events should be characterised in relation to the duration of treatment, the applied dosage, the recovery time, particularly the different age groups (e.g. old and oldest-old patients) and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and electrophysiological recordings (e.g. electrocardiogram).
All adverse events occurring during the course of clinical trials must be fully documented with separate analysis of serious adverse drug events, adverse events leading to drop-outs and patients with a fatal outcome.
Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided, particularly in the patients with mild to moderate cognitive impairment.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of drugs being investigated depending on the action on distinct receptor sites, e.g. cholinomimetic effects of cholinesterase inhibitors. MRIs are needed for monitoring bleeding, signs of inflammation and/or oedema.

7.1. Neurological adverse events

Depending on the dementia subtype special attention should be given to the occurrence or exacerbations of neurological adverse events, particularly cerebrovascular events, extrapyramidal symptoms, disorientation, further impairment of gait, occurrence of seizures, encephalopathy etc. Based on the mechanism of action and target engagement specific neurological adverse events might occur and need special monitoring. Treatment with monoclonal antibodies targeting fragments of β-amyloid has shown to cause amyloid-related imaging abnormalities (ARIA) of various degrees and frequency depending on product activity, dose and patients characteristics. Since the clinical significance of these events is yet to be established, information as to whether a risk management plan (RMP) or simple monitoring is needed, has to be gathered during exploratory trials, where MRI monitoring is mandatory. Also the effect of withdrawal of the test drug should be systematically monitored.

7.2. Psychiatric adverse events

Depending on the dementia subtype specific attention should be paid to the occurrence of hallucinations and other signs and symptoms of affective or psychotic disorders. Other neuro-behavioural abnormalities, particularly disorientation, agitation and aggressive behaviour should be recorded depending on the pharmacodynamic profile of the test drug. Specific claims in this respect, e.g. improvement of neuro-behavioural abnormalities, have to be based on specific studies.

7.3. Cardiovascular adverse events

Depending on the dementia subtype and the pharmacodynamic profile of the medicinal product, its effects on the cardiovascular system (e.g. occurrence of orthostatic hypotension, potential to induce arrhythmias, or increased risk of myocardial infarction) should be monitored.

7.4. Long-term safety

The total clinical experience must generally include data on a large and representative group of patients (see EC Guideline on population exposure), it should be considered that long term safety may be different in the distinct subtypes of dementia, e.g. AD vs. VAD and PDD and the different age groups (younger vs. old and very old). Special consideration must be given to patient populations in early disease stages (preclinical, prodromal), which might be treated for many years in an asymptomatic stage, but certain side effects might be evident.
For the moment, studies on morbidity and mortality are not required before marketing authorisation. However, effects on mortality should be monitored on a long term basis particularly for patient populations in an asymptomatic stage. This will be done post-marketing by implementing a risk minimization or risk management plan.

Definitions

International Working Group (IWG) criteria

a) *Prodromal AD*

Predementia AD is represented by prodromal AD, with episodic memory impairment that is insufficient to disrupt the performance of accustomed instrumental activities of daily living (IADL).

b) *AD dementia*

Indicates that episodic memory loss and other cognitive symptoms are sufficient to interfere with the usual performance of IADL

c) *Preclinical AD*

Refers to the stage of AD that is not clinically expressed; that is, although the molecular pathology of AD is present in the brain, symptoms are absent. The use of preclinical signifies that this stage can only be detected by AD biomarkers, and not by currently available clinical methods. They are further subdivided in

1. Asymptomatic at risk: cognitively normal individual with evidence of AD molecular pathology. It is not known whether progression to symptomatic AD will occur.

2. Presymptomatic AD: individuals with autosomal dominant gene mutations which almost certainly will develop the disease.

IWG-2 criteria for typical AD (A pus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type, based on significantly impaired performa
  - nce on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer´s pathology (one of the following)

- Decrease Aβ1-42 together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- Alzheimer´s disease Autosomal dominant mutation present (in PSEN1,PSEN2, or APP)

IWG-2 criteria for atypical AD (A plus B at any stage)

A Specific clinical phenotype (one of the following)

- Posterior variant of AD (including)
  - An occipitotemporal variant defined by the presence of an early, predominant, and progressive impairment of visuoperceptive functions or of visual identification of objects, symbols, words or faces
  - A biparietal variant defined by the presence of early, predominant, and progressive difficulty with visuospatial function, features of Gerstmann syndrome, of Balint syndrome, limb apraxia or neglect
- Logopenic variant of AD defined by the presence of an Early, predominant, and progressive impairment of single word retrieval and in repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities
- Frontal variant of AD defined by the presence of early, predominant, and progressive behavioural changes including association of primary apathy or behavioural disinhibition, or predominant executive dysfunction on cognitive testing
- Down´s syndrome variant of AD defined by the occurrence of a dementia characterised by early behavioural changes and executive dysfunction in people with Down´s syndrome

B In-vivo evidence of Alzheimer´s pathology (one of the following)

- Decrease Aβ1-42 together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- Alzheimer´s disease Autosomal dominant mutation present (in PSEN1,PSEN2, or APP)

IWG-2 criteria for mixed AD (A plus B)

A Clinical and biomarker evidence of AD (both are required)

- Amnestic syndrome of the hippocampal type or one of the clinical phenotypes of atypical AD
- Decrease Aβ1-42 together with increased T-tau or P-tau in CSF, or increased tracer retention in amyloid PET

B Clinical and biomarker evidence of mixed pathology

For cerebrovascular disease (both are required)

- Documented history of stoke of focal neurological features, or both
- MRI evidence of one or more of the following corresponding vascular lesions, small vessel disease, strategic lacunar infarcts, or cerebral haemorrhages

For Lewy body disease (both are required)

- One of the following: extrapyramidal signs, early hallucinations, or cognitive fluctuations
- Abnormal dopamine transporter PET scan

National Institute on Aging - Alzheimer Association (NIA-AA) criteria

a) Preclinical AD

requires in vivo molecular biomarkers of AD are present, but clinical symptoms are absent.

b) MCI due to AD

requires evidence of intra-individual decline, manifested by

a. A change in cognition from previously attained levels, as noted by self- or informant report and/or the judgment of a clinician.

b. Impaired cognition in at least one domain (but not necessarily episodic memory) relative to age-and education-matched normative values; impairment in more than one cognitive domain is permissible.

c. Preserved independence in functional abilities, although the criteria also accept 'mild problems' in performing IADL even when this is only with assistance (i.e. rather than insisting on independence, the criteria now allow for mild dependence due to functional loss).

d. No dementia, which nominally is a function of c (above).

e. A clinical presentation consistent with the phenotype of AD in the absence of other potentially dementing disorders. Increased diagnostic confidence may be suggested by

(1) Optimal: A positive Aβ biomarker and a positive degeneration biomarker

(2) Less optimal:

(a) A positive Aβ biomarker without a degeneration biomarker

(b) A positive degeneration biomarker without testing for Aβ biomarkers

c) AD dementia

requires

a. The presence of dementia, as determined by intra-individual decline in cognition and function.

b. Insidious onset and progressive cognitive decline.

c. Impairment in two or more cognitive domains; although an amnestic presentation is most common, the criteria allow for diagnosis based on nonamnestic presentations (e.g. impairment in executive function and visuospatial abilities).

d. Absence of prominent features associated with other dementing disorders.

e. Increased diagnostic confidence may be suggested by the biomarker algorithm discussed in the MCI due to AD section above.

Comparison IWG and NIA-AA criteria for clinical diagnosis of Alzheimer´s disease (Morris 2014)

Similarities	
Incorporate biomarkers for AD into the diagnostic process	
Move towards an aetiological diagnosis for MCI	
'Prodromal AD' (IWG)	
'MCI due to AD' (NIA-AA)	
Differences	
IWG	NIA-AA
'AD' refers only to symptomatic stage	'AD' refers to the pathologic process, whether asymptomatic or symptomatic
Replace 'MCI' with 'Prodromal AD'	Retain 'MCI'
Requires objective impairment in memory	Subjective and/or objective impairment in memory and/or nonmemory domains
Biomarker abnormalities required for diagnosis	Biomarker abnormalities support diagnosis but not required

DuBois B *et al. Lancet Neurol* 2010; 9:1118–1127; McKhann GM *et al. Alzheimer's & Dementia* 2011; 7:263–29; Albert M *et al. Alzheimers & Dementia* 2011; 7:270–279; Sperling R *et al. Alzheimer's & Dementia* 2011; 7:280–292.

DSM-5

Major and Mild Neurocognitive Disorders

Major Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
    1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
    2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:

Alzheimer's disease
Frontotemporal lobar degeneration
Lewy body disease
Vascular disease
Traumatic brain injury
Substance/medication use
HIV infection
Prion disease
Parkinson's disease
Huntington's disease
Another medical condition
Multiple etiologies
Unspecified

Mild Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:

Alzheimer's disease
Frontotemporal lobar degeneration
Lewy body disease
Vascular disease
Traumatic brain injury
Substance/medication use
HIV infection
Prion disease
Parkinson's disease
Huntington's disease
Another medical condition
Multiple etiologies
Unspecified

Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).

C. Criteria are met for either probable or possible Alzheimer's disease as follows:

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
2. All three of the following are present:
   a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
   b. Steadily progressive, gradual decline in cognition, without extended plateaus.
   c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present:

1. Clear evidence of decline in memory and learning.
2. Steadily progressive, gradual decline in cognition, without extended plateaus.
3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

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Annex 1

Qualification opinions in AD:

1.Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 14 and t-tau signature and/or PET-amyloid imaging (positive/ negative) as a biomarkers for enrichment,for use in regulatory clinical trials – in mild and moderate of Alzheimer's (EMA/CHMP/SAWP/893622/2011)

2. Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebro -spinal fluid related biomarkers for drugs affecting amyloid burden (EMA/CHMP/SAWP/102001/2011)

3. Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials - in pre-dementia stage of Alzheimer's disease (EMA/CHMP/SAWP/809208/2011)

4. Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment for use – in predementia AD clinical trials (EMA/CHMP/SAWP/892998)

5. Qualification of Alzheimer's Disease (AD) Novel Methodologies/biomarkers for the use of PET amyloid imaging (positive/negative) as a biomarker for enrichment for use in regulatory clinical trials – in predementia Alzheimer's(EMA/CHMP/SAWP/862414/2011)

6. Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/10/WC500151309.pdf

Annex 2

Model of dynamic biomarkers of the AD associated pathological changes (after Jack et al. 2013)