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Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias

Draft

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This guideline replaces '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.

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Table of contents

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 focuses on AD, while other forms of dementia will only be briefly addressed.

The field of AD research and development witnessed a recent paradigm shift in the diagnostic framework of AD which is now considered a continuum with a long-lasting presymptomatic phase, with evidence of AD neuropathology, which precedes 10-20 years the onset of dementia. As the biomarker field is evolving, the possibility to detect disease changes and progression *in vivo*, opens new regulatory scenarios including the possibility to intervene directly on the neuropathology before the appearance of symptoms.

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 While the general approach for symptomatic drug development in mild to moderate and severe AD is still valid, this draft Guidance aims at integrating the requirements for development programs which start earlier in the disease course with the necessary adaptations to the distinct manifestations of the illness at these stages.

The present draft Guidance encompassed the output of the workshop on the clinical investigation of medicines for the treatment of Alzheimer's disease held at EMA on 24-25 November 2014 where current uncertainties around the pathophysiology of Alzheimer's disease (AD), the relevance of biomarkers and the definition of various stages of AD, have been discussed. The document specifically addresses:

- 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 progression rate).
- 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.

As the field is rapidly changing and common knowledge is being built requests for scientific advice on specific recommendations or qualification procedures 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 (McKhann et al., 2011). According to NIA-AA biomarkers are supportive, however not mandatory for diagnosis (see section 5.2.). Both diagnostic criteria use a similar terminology to define three stages in the Alzheimer disease continuum: preclinical AD, MCI due to AD (National Institute of Aging-Alzheimer's Association Criteria, NIA-AA) or prodromal AD (International Working Group, 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 both the IWG and the NIA-AA sets of criteria are accepted for diagnosis of AD for research purposes and for trial enrichment. The standardization and harmonization in the use of biomarkers for different purposes along the course of drug development needs further improvement. In parallel, the development, validation and use of reliable and sensitive instruments to measure cognitive, functional, behavioural and neuropsychiatric symptoms especially in early disease stages are strongly encouraged.

2. Scope

This document aims to provide guidance for the evaluation of any medicinal product for treatment across the AD continuum. In addition, development strategies for disease prevention are addressed. The usefulness of combination therapy targeting multiple pathophysiological mechanisms and their corresponding study designs are discussed.

- Since behavioural and psychiatric symptoms of dementia (BPSD) are highly prevalent in the population of patients with AD stand-alone symptoms including agitation, aggression, depression, anxiety, apathy, psychosis and sleep-wake cycle disturbances are taken into account.

Qualification and/or validation of a certain biomarker as diagnostic tool 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 (see also Annex 1):

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 and different requirements to assess therapeutic efficacy are distinguished according to the stage of the disease (AD dementia, prodromal/MCI due to AD and preclinical AD), the foreseen treatment effect and development goal.

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 new compounds targeting similar or different AD pathophysiological mechanisms are envisaged.

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).

4.2. The main goals of treatment for dementia

The main goals of treatment for dementia are:

- Prevention of symptomatic disease by intervention in suspected pathogenic mechanisms at a preclinical stage.
- Disease modification with slowing or arrest of symptom progression and correlation with evidence of delay in the underlying neuropathological process.
- Symptomatic improvement, which may consist in enhanced cognition and functional improvement (monotherapy or adjunctive therapy)
- Symptomatic treatment of behavioural and psychiatric symptoms of dementia (BPSD)

Since a disease modifying effect correlated with a persistent delay in the underlying neuropathological process is difficult to prove without adequately validated and qualified biomarkers as outcome parameters, a slowing or delay of clinical decline (cognitive and functional) as demonstrated by innovative trial designs may be acceptable as an alternative development goal (see section 8.4.2.).

4.3. Early pharmacology and pharmacokinetic studies

In the early phases of the development of medicinal products for the treatment of AD, it is important to establish the pharmacological mechanism(s) on which the drug may be thought to have therapeutic activity. Characterisation of the primary pharmacodynamic activity of the product (i.e., activity on receptors/neurotransmitters pathways, activity on the amyloid cascade, activity on Tau aggregation; activity on neuroinflammation) will influence the subsequent clinical 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.

In addition to standard pharmacokinetic studies aimed 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. Pharmacokinetic studies of the test-drug in patients with hepatic and /or renal impairment should be performed as appropriate.

The specific characteristics of the mostly older patients have to be taken into account, in particular possible higher sensitivity to the pharmacodynamics of certain medicinal products. 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 as appropriate.

4.4. Exploratory trials

As the research field is rapidly evolving, new targets and novel compounds are being investigated. Unfortunately the field of AD drug development has witnessed many failures and it is noted that in some cases, exploratory trials did not provide 'proof of concept' to inform Phase 3. Consequently the large Phase 3 trials often failed to be confirmatory. Exploratory trials in well-characterized patient populations are therefore strongly encouraged.

The inclusion of the same type of patients at the same stage of the disease in Phases II and III is advised, as safety issues, but also efficacy signals, may not be the same in different subgroups. These studies have the following objectives:

- Demonstration of target engagement
- Assessment of short-term adverse reactions from a clinical and laboratory standpoint
- Determination of pharmacokinetic characteristics
- Determination of maximal tolerated doses
- Determination of PK/PD relationship
- Determination of dose-response
- Preliminary evaluation of efficacy
- Proof of concept

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 progressing considerably and some of them may be used as primary endpoint in proof of mechanism/principle studies.

5. Patient characteristics and selection of population

5.1. Autosomal dominant AD

Autosomal dominant Alzheimer's disease is caused by several known amyloid-related mutations (PSEN1, PSEN2, APP). Patients carrying these mutations are being studied in the Dominantly Inherited Alzheimer Network study and its associated secondary prevention trial. Similar efforts are occurring in an extended Colombian family with a PSEN1 mutation. Interventional and non-interventional projects include monitoring of the disease onset and course and pattern of specific biomarkers change over time from the early completely asymptomatic stages up to the full picture of dementia. Outcome parameters include cerebrospinal fluid (CSF) biochemical markers of AD, positron emission tomography (PET) imaging of brain amyloid deposition and brain metabolism , structural imaging with magnetic resonance imaging (MRI) techniques as well as progressive cognitive and functional impairment (Reiman 2011, Bateman 2012). Patients with autosomal dominant inherited forms of AD, although representing less than 1% of cases, serve as an important model for the development of new therapies and validation of assessment tools. However, the extent to which the pathophysiology of autosomal dominant AD overlaps with sporadic AD remains to be established.

5.2. Sporadic AD

Sporadic AD is a multifactorial disease with a high degree of complexity and represents approximately 99% of AD cases. Neuropathology of AD is characterized by the presence of amyloid beta deposits and tau tangles in neocortical regions of the brain. The pathological process of AD is known to start decades before the onset of clinical symptoms; however the exact relationship between neuropathology and symptoms progression is not yet established.

Validated diagnostic criteria with high sensitivity and specificity are needed to identify homogeneous study populations. Several sets of diagnostic criteria have been developed; despite similarities concerning the definition of earlier disease stages they show important differences.

The IWG criteria (Dubois et al. 2007, 2010, 2014) and the NIA-AA criteria (McKhann et al., 2011; Albert et al. 2011, Sperling et al 2011) similarly distinguish three stages in the AD continuum (preclinical AD, prodromal AD/MCI due to AD, AD dementia) and are fully detailed below (see Definitions).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) the term dementia is substituted with Major and Mild Neurocognitive Disorder (see Definitions). However, there are no DSM 5 criteria available at this time for preclinical AD and biomarkers are not included in the definition.

At this stage NIA-AA 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 and may lead to different study populations:

IWG: objective memory impairment and positive pathophysiological biomarker mandatory

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

In addition, according to the IWG criteria, prodromal AD patients, by definition, do not have any functional impairment not even in instrumental activities of daily living (iADL); while, the NIA-AA criteria accept that patients with MCI due to AD could present with minor problems in performing iADL.

It is not settled yet which criteria are the most sensitive and specific in the clinical setting. From a regulatory perspective the following considerations can be made.

1. For both IWG and NIA/AA sets of criteria, preclinical AD is defined an asymptomatic at risk population where the presence of AD pathology is measured by biomarkers. In this respect, the temporal relationship between amyloid deposit and accumulation and onset of symptoms, is not yet understood and large longitudinal studies are ongoing that may help to validate the diagnostic construct of preclinical AD (see section 9).

2. Any recommendation of diagnostic criteria particularly for prodromal AD/ MCI due to AD is still kept open and all efforts should be focused in detecting a population or homogeneous groups of patients with a defined rate of progression to AD dementia.

It is recognized that the clinical characteristics of patients with prodromal/MCI due to AD may overlap with those at the milder end of the AD dementia spectrum and that, despite all efforts for criteria harmonization, operationally defined stages of disease are not clearly demarcated. In particular, prodromal/MCI due to AD and mild AD patients might have similar cognitive impairment and biomarker values while differentiating for their ability to compensate for the cognitive deficits and for their functional status at baseline. Selection of patients with early AD for long term disease modification trials is complex and should not be unnecessarily subdivided in clinical trials if not justified from a clinical viewpoint. Following this approach, subjects with prodromal AD/MCI due to AD and mild AD may be studied together.

6. The role and type of biomarkers

Biomarkers 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.

While biomarkers for the most part still require validation for many of these particular purposes (Morris 2011), cerebrospinal fluid markers as well as MRI and PET imaging markers are qualified for the enrichment of study populations (see Qualification advices in Annex 1). For the purpose of trial enrichment CSF and PET amyloid biomarkers are strongly correlated, however it is not clear how much this depends on the type of assay and the cut-off, so their use as interchangeable enrichment measures should be justified by data to ensure that a homogeneous population is selected. Although the performance of CSF Aβ1-42 assays has substantially improved, it is also advised to measure not only Aβ1-42 but also T-Tau or P-Tau levels (Medina et al. 2014).

Recently in the diagnostic area the approval in the EU of the radiopharmaceuticals florbetapir (18F), (florbetaben (18F) and flutemetamol (18F) for positron-emission-tomography (PET) imaging of beta amyloid neuritic plaques in the brain have been another step forward. These diagnostic agents are licensed (only in conjunction with a proper clinical assessment) for the use in patients who are being evaluated for Alzheimer's disease versus other causes of cognitive decline, their clinical utility is being evaluated in large observational cohorts.

APOE ε4 status may also be used as a means of enrichment. APOE is the major genotype associated with the risk of developing AD. APOE ε4 homozygotes constitute 2-3% of the population and have a particularly high risk for developing symptoms of late onset AD. However, generalizability will have to be justified if only patients with this specific risk factor are included without any data in non-carriers.

The above mentioned diagnostic criteria for AD incorporate the use of biomarkers which show either the deposition of amyloid products or tau in the brain or CSF, or synaptic or neuronal damage as indicated in reduced glucose metabolism or grey matter atrophy (Villemagne, 2013). 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).

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.

So far, one specific biomarker cannot be endorsed over other alternatives for the purpose of identifying those patients who may progress more rapidly, hence increasing clinical trial efficiency and qualification opinion procedures are encouraged.

To gain evidence for any prognostic or predictive value it would be necessary to test both biomarker positive and negative patients in one study.

Many activities are underway on new biomarkers that may emerge in the future, e.g. Tau PET imaging, biomarkers for neuroinflammation, blood or metabolic signatures (Cavedo et al. 2014; Mapstone et al. 2014; Fiandaca et al. 2014; Villemagne et al. 2015; O´Bryant et al. 2015).

7. Tools for outcome assessment

As a general comment, measurement tools (cognitive, functional or global) should be externally validated, pertinent in terms of realistically reflecting symptomatic severity, sufficiently sensitive to detect changes related to treatment and reliable (inter-rater; test/retest reliability).

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 and functional changes have been suggested, none has convincingly emerged as the reference technique, satisfying the above set of requirements. 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 rater who should is 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. Raters should be trained in advance so that variability is minimised and inter-rater reliability is maximised with the assessment tools used.

Relatively few studies have been performed in patients with severe dementia, so there is a need for adaptation of assessment tools to allow a comprehensive evaluation of the functional and global domains with greater emphasis on ADL and behavioural and psychiatric symptoms of dementia (BPSD).

Efforts are undertaken to develop sensitive and responsive instruments that can be used in earlier stages of AD either by selecting or dropping individual items of known scales such as the ADAS-cog or using specific weighting factors of individual items or both. When applying such approaches it is

important to consider the clinical objective of treating patients and that these objectives are sufficiently captured by the proposed tool. It may be that other items are necessary to demonstrate a clinically meaningful benefit for patients, even if those additional items on average do not change as much over time. Regardless of the approach, new instruments have to demonstrate the capability to measure a relevant clinical construct.

The following section discusses examples for primary and secondary outcomes that have been used in previous trials mostly in dementia stages of Alzheimer disease. The list of endpoints cannot be comprehensive but caveats for the different domains are highlighted. As many others are under further evaluation, the choice of the instrument for assessment and its applicability for early or advanced disease stages should be justified in the study protocol. For new assessment tools a validation plan which includes a prospective study in an independent population should be implemented and scientific advice and qualification procedures are encouraged.

- **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 a standard tool 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. The "Neuropsychological Test Battery for Use in Alzheimer's Disease" (NTB) showed good psychometric properties in the mild to moderate AD population (Karin et al., 2014) and has also recently been used as outcome in a prevention study (Ngandu et al., 2015)

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. The CDR-SB 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.

- **Activities of daily living**

Several scales have been proposed to measure either basic activities of daily living (BADL) which relate to physical activities, such as toileting, mobility, dressing and bathing or instrumental activities of daily living (iADL), such as shopping, cooking, doing laundry, handling finances, using transportation, driving and phoning. 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 and this results in low sensitivity to change of most of the used assessment scales today (Sikkes et al., 2012). The Alzheimer Disease Cooperative Study (ADCS-ADL) has been largely used in clinical trials enrolling patients with mild-to moderate AD, however it failed to detect treatment changes in MCI (Jekel et al., 2015).

Separate measurement tools of ADL/IADL for early and advanced disease stages are needed, and a version of the ADSC-ADL has been already adapted for MCI. The FAQ (Pfeffer et al., 1982) has also been studied in large cohorts (ADNI) and correlated with the likelihood of progressing to AD dementia.

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. In addition, assessment modalities

(informant-report, self-report, performance-based, clinician rated) are often not compared in validation studies.

There is no instrument that can be endorsed over others to best assess even minimal changes in iADL and research should focus on both validating current instruments in specific trial populations or developing new ones concentrating on items known to be affected even in patients with initial cognitive decline. For this purpose, assessing items such as handling finances, keeping appointments, and task accuracy, is suggested, since these items have been shown to be among the most sensitive indicators of early stages of dementia (Jekel et al., 2015).

- **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 for treatment of late stage dementia patients. 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. 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).

- **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 psychometric properties and studies are ongoing to establish their sensitivity to change.

- **Behavioural and Psychiatric Symptoms of Dementia**

The Behavioural pathology in Alzheimer Disease Rating Scale (BEHAVE-AD), the Behavioural Rating Scale for Dementia (BRSD) and the Neuropsychiatric Inventory (NPI) are possible outcome measures; The Cohen-Mansfield Agitation Inventory (CMAI) is specific to agitation in nursing settings. Newer tools are under development reflecting the different characteristic signs and symptoms in accordance with different disease stages (see Section 10).

8. Clinical Trials in Alzheimer´s disease

8.1. Efficacy endpoints in AD Dementia

For patients with **established** AD dementia, efficacy 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 domain. Global assessment should be evaluated as a key secondary endpoint.

In mild to moderate AD it is necessary to demonstrate an effect of treatment both on cognition and on functioning, in order to ensure the clinical meaningfulness of the treatment effect and a co-primary endpoint approach is required.

In severe AD dementia changes in cognitive performance may be less relevant and more difficult to quantify. Hence functional and global domains may be more appropriate as primary endpoints to establish clinically relevant symptomatic improvement in this severely impaired population.

Secondary endpoints of interest may include behavioural and psychiatric symptoms (see section 10). In advanced stages of dementia, behavioural problems with agitation and aggression do occur with major impact on patients and carers.

8.2. Efficacy endpoints in Prodromal AD/MCI due to AD

In earlier disease stages, assessment tools need to be more sensitive and it is recognized that the requirement of two co-primary endpoints addressing cognition and functional activities of daily living (ADL) might be difficult. However, it is still necessary to demonstrate the clinical relevance of the results.

The use of two co-primary endpoints assessing cognition and function is a suitable approach in this population, however a number of difficulties and limitations of currently available instruments are recognized.

Currently used cognitive scales have demonstrated a ceiling effect which makes them not sensitive enough to detect small changes in cognition and complex neuropsychological batteries may be difficult to implement in large clinical trials.

In addition, patients who are closer to the onset of dementia have subtle but already noticeable impairments in their daily functioning, however, extent to which each single individual is capable to compensate for his/her cognitive deficit and adjust its daily activities is very variable. The progression of the functional deficit may be very slow creating feasibility issues (sample size estimation and power of the study) with currently available scales.

Constructing more sensitive item scoring for MCI-specific scales and/or investigating in detail only those domains that have been shown to be impaired consistently in MCI due to AD/prodromal AD, such as financial capacity or "new" technology skills, could solve the problem (see above).

Alternatively, a composite scale with a combined assessment of cognition and its impact on daily functioning, could be used as single primary endpoint in this population.

However, the possibility to combine both cognition and function in one single primary endpoint should not limit the effort to pursue a comprehensive assessment of the significant contribution of both domains to the detectable treatment effect. In addition, measures of cognition and function, instrumental activities, executive functions and health related quality of life should be included as secondary endpoints to contribute to the overall assessment of efficacy. It is recognized that not all of these objectives may be achievable. Nevertheless it remains important to establish that the demonstrated effects of treatment are clinically relevant.

8.3. Efficacy endpoints in Preclinical AD

For the time being there is no "gold standard" for assessment of treatment effect in patients with preclinical AD (see section 9). Cognitive endpoints used in primary and secondary 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. Novel outcome tools sensitive to small neuropsychological changes in this population are being developed, however they are not yet validated and cannot be endorsed solely as primary endpoints in this population. A time to event analysis could be a complementary measure in order to obtain a clear definition of responders and non-responders to support the relevance of any chosen outcome, although feasibility issues including length of the trial and number of drop-outs are recognized. Until a biomarker will be qualified as a reliable surrogate measure of treatment effect in absence of a clinically observable change, patients should be followed up for a sufficient time to capture relevant cognitive changes.

8.4. Trial Design Features in Alzheimer's Disease

8.4.1. Symptomatic treatments

Symptomatic improvement is defined as a treatment effect that is temporary and static over time and that does not change the overall course of the disease. The study should be designed to show statistically significant differences in both cognition and function depending on disease stages as described above. The effect of treatment should be illustrated as change from baseline. In addition, a definition of response could be provided, in terms of the proportion of patients who achieve a pre-defined clinically meaningful benefit (response). Responder criteria need to be chosen carefully, taking account of the natural progression of disease over the course of the trial, e.g., responders might be

defined as improved to a relevant pre-specified degree in the cognitive endpoint and at least not worsened in the two other domains (function and global).

It is acknowledged that the feasibility of long term placebo controlled monotherapy studies has become seriously limited in mild to moderate and severe AD due to the availability of several symptomatic treatments. However, since substantial differences between placebo patient populations 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 symptomatic treatment options. In order to minimize the ethical concerns for the use of placebo, a placebo controlled trial in which subjects are permitted to take standard therapy if clinically indicated could be considered, depending on the nature of the new product. Stratification according to baseline background therapy should be undertaken and it would typically be advantageous to include sufficient patients with no baseline background therapy in order to allow for an evaluation of the new product as monotherapy.

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 is unlikely to be acceptable as pivotal evidence of efficacy.

For prodromal AD/MCI due to AD no products are approved, so placebo is the comparator of choice.

Study duration will be highly dependent on the studied patient population, clinical trials in mild to moderate AD patients have been traditionally of 6 months duration.

On-treatment follow-up of at least 12 months is recommended (see section 14). 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.

If the new treatment is intended to be used exclusively as add-on to standard symptomatic treatment (e.g. AChEI) a simple two way placebo controlled add-on study is the appropriate design. Long term maintenance in the add-on setting can be demonstrated with a randomized withdrawal design.

8.4.2. Disease modifying treatments

A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes. This can be demonstrated by results that show slowing in the rate of decline of clinical signs and symptoms and when these results are linked to a significant effect on adequately validated biomarkers. Such biomarkers should reflect key pathophysiological aspects of the underlying disease process based on a plausible disease model.

Placebo-controlled trials are mandatory as long 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.

Trial duration should be relevant to the treatment goal. 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 . Depending on the product's mechanism of action, the timing of the intervention might be critical to the outcome. If efficacy is demonstrated in prodromal/MCI due to AD patients in a disease modifying trial, it would be difficult to extrapolate information on treatment initiated at a later stage of the disease course (moderate or severe dementia). Ideally, efficacy should be demonstrated in two trials at two different stages along the AD continuum. Alternatively, if efficacy is demonstrated in a single trial, patients should be followed up for a sufficient time to inform effect in subsequent stages.

A hypothesis of disease modification seems most consistent with a statistical comparison of rates of change in clinical symptoms over time (slope analysis) between treatment groups. 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 pharmacologically reversible effect that increases over time could also lead to such an outcome. In consequence clinical outcomes in a parallel group design should be measured at regular intervals to establish a clinically relevant effect. A slowing in rate of decline over time in the pre-specified endpoints should be established at (at least) two distinct time points. Such a study should ideally be enhanced with a phase of delayed-start or withdrawal design. With those designs the length of follow-up is critical since a too short follow-up could show a difference when the curves are actually still coming together.

Alternatively, the possible disease modifying effect may be addressed by a time-to-event approach. A time to a pre-specified decline on a clinically relevant endpoint may be preferred in earlier disease stages to support the relevance of outcomes since symptoms will be minimal and changes over time might be difficult to assess. The event in question must be an event of clear clinical importance (e.g. time to dementia) and not simply defined in terms of decline on a rating scale (e.g. a 2 point decline in ADAS-cog). The time before patients are expected to reach this event must be substantial and the difference between treatment groups in the median time to event must be of a magnitude that could not plausibly be attributable to a symptomatic effect. The described 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, sensitivity of endpoints over time, 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.

Evidence of delay in rate of decline, should be accompanied by evidence of a delay in the progression of brain neurodegeneration as shown by a biomarker program.
Since, at present, biomarkers are not validated as outcome parameters, the choice of biomarker as well as the type of analysis is left open, although more weight will be given to those biomarkers showing, not only target engagement, but also an effect on the downstream disease mechanisms.
In case correlation with relevant biomarkers is unclear, evidence of change in the disease course supported by an innovative study design as those suggested above together with suitable analyses, could be acceptable as an alternative treatment goal such as "delay or slowing in rate of decline" if efficacy in cognition and function is demonstrated (see section 4.2.).

8.4.2.1. Combination of disease modifying treatments

Since the pathophysiology of AD is known to be multi-factorial, it might be anticipated that combinations of disease-modifying treatments with complementary mechanisms of action may have an

important therapeutic role. If two disease-modifying drugs are studied in combination there is conventionally a requirement to show the contribution of each drug to the targeted mechanisms of action and to clinical efficacy separately for each drug. Typically this would require a trial in which the combination is compared to the two monotherapy arms and to placebo where appropriate. 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 scientifically justified and the appropriateness of the approach will be evaluated case by case. Since these strategies are new, scientific advices are encouraged.

9. Development strategies for disease prevention

The overall goal of primary prevention in dementia is to reduce the incidence of the disease in the target population. The goal of secondary prevention is to prevent a disease at a preclinical state from progressing to a later more manifest stage.

Population for prevention trials can be enriched based on genetic markers (APOε4 status, see section 6; for autosomal dominant mutations see section 5.1), biological markers (Aβ and tau CSF levels or retention of amyloid or tau tracers at PET) or environmental risk factors (vascular or metabolic).

AD is a multifactorial disorder, however the relative contribution of each risk factor to the onset of the disease is not yet established and it is difficult to translate population risk at an individual level. Currently there are several ongoing RCTs using multidomain interventions (exercise, management of metabolic and vascular risk factors, cognitive training, nutritional advice) for prevention of cognitive impairment and AD dementia. Initial findings from the FINGER trial (Ngandu et al., 2015) suggest that targeting multiple risk factors simultaneously leads to a protective effect in cognition. The European Prevention Initiative (www.edpi.org), also aims at bringing new insights into the design of prevention trials and in addition, prevention trials focusing on lifestyle related factors are ongoing worldwide (PREVENT-Alzheimer and PROMoTE in Canada and AIBL in Australia).

Pharmacological interventions directed to suspected pathophysiological mechanisms underlying AD at a pre-symptomatic stage are considered a reasonable approach for prevention strategies. Placebo controlled trials should be carried out in enriched populations; however the diagnostic construct of preclinical AD as well as the disease model in such an early stage still need to be validated and issues of inter-individual variability and contribution of other risk factors to the progression rate should be considered. The time course from the accumulation of AD pathology and the onset of clinical symptoms is not yet established and the capability of the brain to respond and adapt to structural changes differs largely among individuals (cognitive reserve) and even varies from day to day in any given patient. For these reasons, from a regulatory perspective, the main goal of treatment in at risk population remains prevention of cognitive impairment, since no biomarker can be yet considered a valid surrogate endpoint.

Prevention trials require large samples and long follow up, typically of at least 5 years. However, since scientific information to provide a firm regulatory framework for prevention trials is still lacking, no firm recommendation can be made and therefore scientific advice is recommended in case this is pursued.

10. Behavioural and Psychiatric Symptoms of Dementia

In general symptomatic treatment of AD includes also treatment of behavioural and psychiatric symptoms of dementia (BPSD) like agitation, aggressive behaviour, apathy, psychosis (delusion and hallucinations), depressive symptoms, anxiety and sleep disorders. Although not included in the formal

diagnostic categorization of AD, BPSD are highly prevalent in the population of patients with AD, 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. BPSD are intrinsically variable and fluctuating along the course of the disease and issues of "pseudospecificity" should be considered. While clusters of behavioural symptoms like agitation and aggression are more prevalent in advanced stages of dementia, clusters of mood symptoms like depression and apathy are more common in earlier stages. Whether the aggregation of symptoms and clusters is empirical or supported by a biological plausibility remains to be established, therefore the possibility to target a single symptom or cluster of symptoms in the context of BPSD has to be justified by a strong rationale and would depend on the drug mechanism of action.

10.1. Efficacy endpoints for behavioural and psychiatric symptoms of dementia

In order to be considered as a stand-alone indication, symptomatic treatment of BPSD should be addressed in a separate trial. This requires reliable and valid measurement tools for the studied patient population in the specific stages of the disease. Several rating scales have already been used in clinical trials, they should be chosen on the basis of the target symptoms and the population under study (see section 7). The development of sensitive tools for behavioural and psychiatric symptoms in earlier stages of dementia is encouraged. Cognition and function should be measured in these trials as secondary endpoints in order to exclude a deteriorating effect on these domains. BPSD should also be evaluated as secondary endpoints in trials targeting cognition and function as primary outcomes, however a stand-alone indication cannot be extrapolated in this case.

10.2. Design features for trials in behavioural and psychiatric symptoms of dementia

A parallel two-arm placebo controlled trial with non-pharmacological treatment as background therapy should be the design of choice in evaluation of BPSD. This also holds true for agitation studies considering that risperidone is only licensed for short-term treatment due to specific safety concerns in this older population. It is acknowledged that non-pharmacological treatments for BPSD are effective and represent standard of care; moreover environment has a strong influence on treatment outcome. Both non-pharmacological treatment and environment are highly variable across sites and should be standardized as much as possible in the context of a clinical trial. For symptomatic treatment of BPSD in dementia stages of AD a duration of 8 to 12 weeks is recommended, however study duration depends on the symptoms and their fluctuation and should be justified. Treatment may be prolonged in clinical practice and longer term data are required to address maintenance of efficacy, rebound effect, discontinuation phenomena and safety. An open label extension phase may not be sufficient if severe issues of safety arise in this vulnerable population, in this case a parallel arm would be required.

11. Statistical considerations

As for any trial it is of critical importance to clearly specify the scientific question of interest that the trial seeks to address. This should consider, explicitly, post-randomisation events such as patient withdrawals from randomised treatment or from protocolled follow-up, and use of alternative therapeutic interventions. 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 in respect of a particular scientific question of interest. Also, several approaches that are standard in other conditions perform extremely badly here.

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 would mean that patients who withdraw early are likely to be 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 scientific question of interest to which this method appears to most closely relate, even if this has not been clearly specified in trial protocols. To assess the treatment effect in a hypothetical scenario that all patients can and will take the treatment as directed is not of primary interest since the impact 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 a routine approach to the primary analysis because of this concern that the results would tend to overestimate the true treatment effect.

Slope based analyses are also problematic in the presence of early withdrawals if they assume the same slope after patient discontinuation as before.

Alternative choices of primary analysis method should also be considered. 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.

Notwithstanding the attendant risks of bias arising from differential patient dropout, methods using placebo data to impute missing values in the active arm could be useful, as could other modelling of the expected loss of effect after treatment discontinuation. Tipping point analyses which explore how bad the results for patients with missing data would have to be before a positive result is lost could be conducted. Whatever choice is made must be prespecified and fully justified in the protocol.

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.

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.

Different considerations apply if the objective of the analysis is concerned with the theoretical nature of a treatment effect rather than establishing the expected benefit of treatment in the population. An example of such a situation is the analysis of data from a delayed-start period where the objective is to evaluate whether delayed start patients would “catch up” to early start patients if both groups continue treatment. In these situations use of an MMRM type approach to the analysis could be justified.

12. 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.

13. 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.

14. 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 a fatal outcome.
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 or enzymes, e.g. cholinomimetic effects of cholinesterase inhibitors. MRIs are needed for monitoring amyloid related imaging abnormalities (ARIA) such as bleeding (ARIA-H), signs of inflammation and/or oedema (ARIA-E) and skin examinations are recommended for BACE inhibitors.
In short term trials, on treatment follow up of at least 12 months beyond the double blind phase is recommended. This can be achieved with an open label trial extension in patients considered as responders and desiring 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 and to estimate the maximal duration of the symptomatic effects.

14.1. 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, product target, dose, and patients characteristics (APOε4 status or others). Depending on the nature and specific binding characteristics of the antibody the risk for ARIA-E may be less likely. 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.

14.2. 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.

Overdose and suicide

Depending on the mechanism of action risks and effects of overdose should be studied, therefore the potential for the test product to precipitate suicidal thoughts and behaviour should be actively measured using validated rating scales (e.g. InterSePT Scale for Suicidal Thinking, Columbia Suicidality Severity Rating Scale (C-SSRS) or other validated instruments). Rates of suicidal events (from suicidal

ideation to completed suicide) should be presented and narrative summaries of suicidal patient statements or behaviours should be provided.

14.3. 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, the potential to induce arrhythmias, or increased risk of myocardial infarction should be monitored.

14.4. 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 adverse reactions 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 and a 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 performance 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 1-42 and t-tau and/or PET-amyloid imaging (positive/ negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease (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 clinical trials for regulatory purpose - 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/892998/2011)

5. Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease (EMA/CHMP/SAWP/567188/2013)

Annex 2

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