EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 February 2018
CPMP/EWP/553/95 Rev.2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

Draft agreed by CNSWP	December 2015
Adopted by CHMP for release for consultation	28 January 2016
Start of public consultation	01 February 2016
End of consultation (deadline for comments)	31 July 2016
Agreed by CNSWP	December 2017
Adopted by CHMP	22 February 2018
Date of coming into effect	1 September 2018

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

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

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.

This document focuses on AD, while other forms of dementia will only be briefly addressed. Among the aetiological hypotheses, the amyloid cascade hypothesis has been central in drug development, however, other theories about AD have been postulated.

For regulatory purposes high specificity but also high sensitivity of diagnostic criteria will be needed.

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 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 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.).
- Targets of estimation defining treatment effects of interest for regulatory decision making
- Design of long term efficacy (maintenance of effect) and safety studies.

As the field is rapidly changing and common knowledge is being built there are still quite significant uncertainties and hence, firm recommendations on the clinical development cannot be given; 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. 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.

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 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, 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 sensitivityand specificity of the diagnostic criteria of AD by reducing the level of uncertainty. However, AD and non-AD dementia show overlapping clinical and neuropsychological profiles that are not always easy to distinguish.

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 improvementin terms of consistency and alignment. 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.Specific recommendations for other types of dementias are beyond the scope of this document and will be only briefly addressed in Section 4.2.2. In addition, development

strategies for AD 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))
- Guideline on adjustment for baseline covariates in clinical (EMA/CHMP/295050/2013)
- Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1)
- 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))
- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**)
- Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005)

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 and Qualification of novel methodologies for drug development: guidance to applicants (EMA/CHMP/SAWP/72984/2008).

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

4.2.1. Alzheimer´s disease

The main goals of treatment for AD 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 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 as demonstrated by innovative trial designs may be acceptable as an alternative development goal (see section 8.3.2.).

4.2.2. Other dementias

A large proportion of patients with dementia show evidence of multiple overlapping neuropathological processes. Specific guidelines for other types of dementias such as vascular dementia, Lewy body dementia, fronto-temporal dementia or other rare conditions associated with dementia such as Huntigton´s disease or Down´s syndrome are currently not available and scientific advice is recommended for more detailed recommendations.

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 healthy volunteers, if available and relevant, might give some estimation of the appropriate dose range.

Where applicable, 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.If the hypothesis regarding the mechanism of action requires so, information of drug penetrance through the blood brain barrier and target engagement in the brain will be important aspects to interpret trial outcome.

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 expectedand/or the route of administration limits interactions with other medicinal products. 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 given often concurrently with the test product in this population (including psychoactive, antiplatelet and lipid metabolism agents).

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 to be conducted prior to phase 3.

Exploratory studies may 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
- Identification of subsets of patients able to benefit from treatment and population selection for confirmatory trials

The duration of such trials will depend either upon the time to measurable response that is expected, or the parameter(s) 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. However, it is suggested to collect also clinical data in exploratory trials, to inform how they can potentially be further used in subsequent pivotal trials (see sections 3, 6 and Annex 1).

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 adaptive 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. The factors influencing symptom onset and progression in ADAD are not fully understood.Patients with autosomal dominant inherited forms of AD, although representing less than 1% of cases, may serve as an important model for the development of new therapies and validation of assessment tools. However, the extent to which the pathophysiology and the response to therapy of autosomal dominant AD overlap 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 and specific outcome measuredis not yet established.

Validated diagnostic criteria with high sensitivity and specificity are needed to identify homogeneous study populationsacross the disease spectrum. The purely clinical NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer´s disease Related Disorders Association) have been revised to incorporate biomarkers of AD pathology. Several sets of diagnostic criteria have been developed; despite similarities concerning the definition of earlier disease stages they show important differences.

The IWG criteria and the NIA-AA criteria similarly distinguish three stages in the AD continuum (preclinical AD, prodromal AD/MCI due to AD, AD dementia) and are 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. 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. Both criteria include atypical (IWG) or non-amnestic (NIA-AA) presentations 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. Preclinical AD is defined as an asymptomatic population where the presence of AD pathology is measured by biomarkers (both Aβ and Tau markers; see Definitions). In this respect, the temporal relationship between amyloid deposit and accumulationor evidence of tau pathology 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.
3. Enrichment strategies are recommended to identify and characterize patients at high risk to develop clinical AD during the trial (see section 6).

It is recognized that the clinical characteristics of patients with prodromalAD/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, prodromalAD/MCI due to AD and very mild AD patients (early AD) 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.Pre-specified patient stratification should be based on clinical features, biomarkers and diagnosis. Selection of patients with early AD for long term interventional trials is complex and should not be unnecessarily subdivided 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 (see sections 8.2 and 8.3.2).

5.3. Mixed Dementia and Mixed AD

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 as mentioned above 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 (see Definitions).

6. The role and type of biomarkers

Biomarkers in AD clinical trials can be separated according to their potential context of use:

- diagnostic – for determining diagnosis (see section 5.2);
- enrichment – for selecting populations;
- prognostic – for determining course of illness;
- predictive – for predicting a future clinical response to therapy and for safety assessment;
- pharmacodynamic – for determination of intended or unintended activities.

While biomarkers for the most part still require validation for many of these particular purposes, cerebrospinal fluid markers as well as MRI and PET imaging markers are qualified for the enrichment of study populations (see Qualification opinionsfor specific populations in Annex 1). Context of use of these biomarkers remains to be qualified in preclinical AD.

Amyloid PET and CSF Aβ42 are measuring different aspects of amyloid biology: (1) fibrillar aggregates of Aβ for PET and (2) soluble Aβ42 monomer levels which are only indirectly related to plaques, for CSF Aβ42. 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, or different underlying biological processes that these methods are capable of probing their use as interchangeable enrichment measures should be justified by data to ensure that a homogeneous population is selected.Assays operating characteristics should be specified when known. Although the performance of CSF Aβ42 assays has substantially improved it is also advised to measure not only Aβ42 but also total Tau (t-Tau)or phospho-Tau (p-Tau levels). Aβ42 and Tau ratio was found to have a higher positive predictive value than Aβ42 alone (see EMA/CHMP/SAWP/102001/2011; Annex 1).

The approval in the EU of various radiopharmaceuticals for positron-emission-tomography (PET) imaging of beta amyloid neuritic plaques in the brain hasbeen another step forward. These agents are licensed (only in conjunction with a proper clinical assessment)to assist in the diagnosis of AD in patients who are being evaluated for Alzheimer's disease andother causes of cognitive impairment. Their clinical utility is being evaluated in large observational cohorts.While thresholds for categorizing subjects as amyloid positive or negative can be converted between tracers with a high level of consistency their interchangeable use for other purposes (e.g. quantification of changes) still needs to be established. Results from quantitative amyloid imaging in autosomal dominant AD may also give insight on the most promising technique to detect longitudinal changes of amyloid burden in sporadic AD.

APOE is the major genotype associated with the risk of developing AD.APOE ε4 homozygotes constitute 2-3% of the general Caucasian population and have a particularly high risk ofdeveloping symptoms of late onset AD, more so in the presence of AD pathology. APOE ε4 status may be used as one of themeans of enrichmentin a clinical trial population. However, generalizability will have to be justified if only patients with this specific genotype are included without any data in non-carriers.

The above mentioned diagnostic criteria for AD (see section 5.2) incorporate the use of biomarkers which show either the deposition of amyloid products or tau in the brain or change in levels of these proteins in CSF, or synaptic or neuronal damage as indicated in reduced glucose metabolism or grey

matter atrophy. While the core clinical criteria remain the main landmark of the diagnosis of AD in clinical practice (DSM-5), biomarkers may increase the accuracy of the diagnosis.

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. The trajectory of cognitive decline may further be modified by cognitive reserve, medical comorbidities, lifestyle factors and cognitive training (see section 9). Hence increasing clinical trial efficiency and qualification opinion procedures are encouraged.

Qualification of biomarkers for any of the above mentioned use requires to test both biomarker positive and negative patients.

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.

7. Tools for outcome assessment

Cognition, function and global assessments cover key domains in the evaluation of AD patients (see sections 8.1.-8.3). Health related quality of life tools, both generic and disease specific, should also be included. Behavioural and psychiatric symptoms of dementia (BPSD) are not included in the diagnostic criteria (see section 5.2) but are very common across the AD spectrum and constitute an important symptomatic outcome (see section 10.).

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

It is recommended that each domain is assessed by a rater who 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.It is preferable that the rating clinicians are not otherwise involved in the conduct of the clinical trial. Raters should be trained in advance so that variability is minimised and inter-rater reliability is maximised with the assessment tools used.Ideally, rater training for the different domains should be standardised on a national and international basis to reduce score variability.

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) (see section 8.2).

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 or using specific weighting factors of individual sub-tests or both.

These development excercises are supported by cognitive functional composite measures, derived with appropriate methodology and showing an increased magnitude of change in comparison to their cognitive counterparts in prodromal AD. If composite scores are used, the individual item/dimensions should also be quantified.

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. Some items or sub-tests may be 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.

Items of activities of daily living such as handling finances, keeping appointments, task accuracy and technology skills, have been shown to be among the most sensitive indicators of earlier stages of dementia rather than basic self-care or instrumental activities such as shopping, doing laundry or cooking that are more sensitive in advanced stages.

Some components of currently used instruments, especially cognitive measures, are more sensitive to detect disease progression in earlier stages of AD (e.g. world recall, world recognition, executive functions).

The outcome measures should ideally bear some relevance to existing tools for which historical experience exists and which should also be included where appropriate.

A validation plan, ideally including a prospective study in an independent population, should be implemented and scientific advice and qualification procedures are encouraged.

8. Confirmatory Trials in Alzheimer´s disease

As for trials in any disease area it is of critical importance to clearly specify the scientific question(s) of interest that the trial seeks to address.

8.1. Intercurrent events in Alzheimer´s disease

Choices made for trial design, data collection and statistical analysis (see section 11) should be aligned to the scientific question of interest that is posed by the trial objective. This requires a detailed specification of the estimand (the “target of estimation” or, simply, “what is to be estimated”), including the specification of strategies to handle each of the relevant events that occur after randomisation and that would affect the interpretation of an outcome variable or preclude its observation (intercurrent events). Intercurrent events could include, but might not be limited to, discontinuation of treatment, use of non-investigational medications including protocolled ‘rescue’ medications, behavioural treatments, the occurrence of events not primarily related to AD or treatment and death. Particular attention should be given to the expected incidence of different intercurrent events and their relationship to the interpretation or the observation of the outcome variable.

In general, and unless an alternative is duly justified, the actual adherence to treatment should be reflected in the target of estimation (i.e. the “treatment-policy” strategy should be applied for this intercurrent event).

Considerations about other intercurrent events to be addressed, and the preferred strategies to address them, might be influenced by different factors. These include, the stages of AD studied, the

symptom domain(s) and the domain(s) covered by the primary outcome measurement tools (for example, intercurrent events that would affect the interpretation of an outcome on behaviour but not an outcome on cognition would only need to be addressed for trial objectives related to behaviour).

The preferred choice of strategy to reflect each intercurrent event might also differ depending on the question of interest (e.g. demonstration of a treatment effect vs. establishing a disease modifying effect of treatment).

In the following sections some points to consider when deciding on strategies for relevant intercurrent events are discussed. These are examples and do not represent a comprehensive list. Sponsors are encouraged to discuss both the target of estimation and an aligned method of estimation (the approach to statistical analysis) at scientific advice. To give context to these discussions, the types and frequencies of important intercurrent events expected should be estimated.

8.1.1. Target of estimation in AD dementia

In the moderate-severe AD setting, values for outcome variables at the end of the scheduled follow-up can be thought of as providing different information according to whether or not the patient has discontinued treatment and whether or not the patient has initiated concomitant treatment.

Since patients are not expected to continue deriving benefit once treatment is discontinued the effect of treatment regardless of discontinuation of treatment is normally an appropriate strategy for the primary target of estimation. A supplementary analysis targeting the amount of treatment discontinuation would also be of interest.

Patients can be expected to initiate new medication or to modify the dose of concomitant symptomatic treatments, with or without discontinuing assigned treatment. The impact of those medication changes complicates the evaluation of the effect of the test product compared to placebo or active control. Therefore, providing that reliable methods of estimation can be identified, an appropriate target of estimation could be based on a hypothetical scenario in which the new concomitant medication or modifications in the dose of concomitant medications had not been introduced. Again, supplementary analyses targeting the types and amounts of other medications used would be of complementary interest.

Especially if long trials in rather advanced stages of AD dementia are conducted, death is likely to occur in a proportion of patients. In this case, justification is expected on how death should be addressed in the estimand. The reasoning to be made around the choice of strategy might rely implicitly or explicitly on assumptions about the absence or presence of a treatment effect on survival that will need to be investigated.

8.1.2. Target of estimation in the prodromal AD / MCI due to AD or Preclinical AD setting

In the prodromal/MCI setting, patients are not from the beginning of the trial on a standard background therapy. The initiation of a non-investigational symptomatic treatment should be regarded as an intercurrent event that will influence the measurement of the outcome variable and as such is to be addressed in the estimand. As above, the treatment effect ‘if symptomatic medications had not been introduced’ could be an appropriate target of estimation, providing that reliable methods of estimation can be identified. An alternative strategy might be to integrate the event in the outcome (e.g. to define a non-responder as a patient with a certain degree of progression or who uses additional symptomatic medication).

In the preclinical AD setting it is anticipated that trials are planned to be of long duration and the number of patients discontinuing treatment could be significant. Again, the actual adherence to treatment should be reflected in the target of estimation (i.e. the effect of treatment "regardless of discontinuation"). In principle, understanding the effect of treatment in a stratum of patients, for example those who can remain on experimental treatment over the long period of time thought to be needed for the intervention to be effective, is of particular interest in this setting, though choices for trial design and analysis to obtain a reliable estimate are not obviously available. An 'observed case' type approach is inadequate. A wide range of events not related to AD or treatment, but thought to influence the measure of outcome (cognition) during the trial period should be regarded as relevant intercurrent events (e.g vascular or cardiac or metabolic events not related to the intervention but related to the outcome) to be addressed in the specification of the estimand.

8.2. Efficacy endpoints in Alzheimer´s Disease

8.2.1. Efficacy endpoints in AD Dementia

For patients with **established** AD dementia, efficacy should be assessed in the following 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.

In mild to moderate AD to accept an effect on cognition it should be clinically meaningful. The clinical relevance should be confirmed by an effect on function or clinical global assessment in a co-primary endpoint approach.

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

Secondary endpoints of interest in AD dementia may include health-related quality of life scales and behavioural and psychiatric symptoms.If BPSD is a primary target a separate trial is mandatory (see section 10).In advanced stages of dementia, behavioural problems have a major impact on patients and carers.

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

In earlier disease stages, the use of two co-primary endpoints assessing cognition and function or global might be difficultdue to the limitations of currently available instruments. However, it is still necessary to demonstrate the clinical relevance of the results. This applies also when patients with prodromal AD/MCI due to AD and patients with mild AD are studied together in one study (see section 5.2).

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, the 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, could be the way forward.

The use of a composite scale with a combined assessment of cognition and its impact on daily functioning as a single primary endpoint is also considered appropriate 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, 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.

8.2.3. 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 support the relevance of any chosen outcome, although feasibility issues including length of the trial and number of drop-outs are recognized. The event must be of clear clinical importance such as onset of cognitive impairment (see section 9). 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.

8.3. Trial Design Features in Alzheimer's Disease

8.3.1. Symptomatic treatments

Symptomatic improvement is defined as a treatment effect that does not change the overall course of the disease. Studies should be designed to demonstrate a treatment effect in both cognition and function or clinical global assessment depending on disease stages as described above (see sections 8.1 and 8.2). The effect of treatment should be demonstrated as change from baseline. In addition, a definition of trial success could be provided, in terms of the proportion of patients who achieve a 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 recommended 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, imbalanced randomisation could be acceptable.

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.

If the new treatment is intended to be used exclusively as add-on to standard symptomatic treatment (e.g. AChEI) a simple two-arm placebo-controlled add-on study is the appropriate design.

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. Controlled clinical trials in mild to moderate AD patients have been traditionally of 6 months duration.

On-treatment long-term follow-up for safety of at least6 months is recommended after the double-blind phase (see section 13). 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

8.3.2. 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 at randomization.

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 and prodromal AD/MCI due to AD, minimum duration of 18 months has been assumed to be sufficient, in some trials, 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.

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 would usually be expected to be established incorporating multiple time points in a model-based analysis. The model used and hypotheses tested should be justified (see also section 11).

Such a study should be enhanced with a phase of delayed start, with the intention of showing that the difference in clinical measures between delayed-start patients and those who started treatment early is maintained throughout the study. With this design the length of follow-up and the parameters of the analysis are 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.

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. Different considerations on the target of estimation compared to analyses showing a treatment effect could apply (see section 11).

Evidence of slowing or delay of clinical 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 interpretation of relevant biomarker changes 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 (see section 4.2.1).

8.3.2.1. Combination of disease modifying treatments

Since the pathophysiology of AD involves multiple pathways which could 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 (e.g. APOε4 status, see section 6; for autosomal dominant mutations see section 5.1), biological markers (e.g. Aβ and tau CSF levels, retention of amyloid or tau tracers at PET, etc.) or environmental risk factors (e.g. 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.

Several RCTs or prospective cohort studies are ongoing, which will soon bring new insights into the design of prevention trials (e.g. EPAD, PREVENT-Alzheimer and PROMoTE in Canada and AIBL in Australia). Initial findings from the FINGER trial (Ngandu et al., 2015) suggest that targeting multiple risk factors simultaneously leads to a protective effect in cognition. 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 3 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 could 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 should be the design of choicein evaluation of BPSD. It is acknowledged that a new investigational drug could be evaluated on top of standard of care which consists of non-pharmacological and pharmacological treatments, even though risperidone is only licensed for short-term (6 weeks) treatment of persistent aggression due to specific safety concerns in this older population. Moreover,environment has a strong influence on treatment outcome.Standard of care is highly variable across sites and all efforts should be done to reduce the variability 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 effects, 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

11.1. Analyses aimed at demonstrating a treatment effect

Choices made for statistical analysis, including the handling of missing data, should be aligned to an agreed target of estimation. The primary analysis will be associated with various assumptions which can be examined through a sensitivity analysis aligned to the same target of estimation. Supplementary analyses, possibly aiming at other targets of estimation, can also assist in the interpretation of trial data.

Efforts should be made to collect all data that are relevant to support a statistical analysis aligned to the important targets of estimation. The occurrence of intercurrent events such as discontinuation of treatment or use of additional medication does not imply that the variable cannot be measured thereafter, unlike for terminal events such as death. In particular, occurrence of an intercurrent event

does not imply that all data planned to be collected thereafter should be regarded as 'missing'. For example, where required for estimation efforts should be put in place to continue data collection even after patients discontinue treatment (discontinuation of randomised treatment should not be conflated with withdrawal of a patient from follow-up). Having specified the data to be collected in respect of a particular estimand, failure to collect the required data results in a missing data problem for subsequent statistical inference.

The handling of missing data, particularly resulting from patients who discontinue from the trial, is of particular concern in Alzheimer's disease trials as several approaches that have been used regularly in other conditions present problems in conditions with a deteriorating clinical course. In particular, methods such as last observation carried forward (LOCF) and baseline observation carried forward (BOCF) are inappropriate, not only because of known limitations of these single-imputation approaches, but 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 is also questionable if implemented based on use of observations from patients who continue on treatment to model the unobserved (missing) response in patients who have discontinued from treatment, where the target of estimation is the treatment effect regardless of discontinuation of the assigned treatment. Analogously, slope-based analyses are also problematic in the presence of early withdrawals if they assume the same slope after patient discontinuation as before.

Modelling based on information from patients treated with placebo seems more appropriate in general, though for patients assigned to experimental treatment modelling based on those patients continuing in the trial despite discontinuation of assigned treatment might be more appropriate depending on the target of estimation. In both approaches, the attendant assumptions would have to be addressed through a sensitivity analysis.

Other analytical approaches can be considered not only to handle missing data, but also to alter the impact of discontinuation of treatment or use of additional medication. Specifically, these intercurrent events might be integrated with the variable to form a responder analysis e.g. to target estimation of a treatment effect on the proportion of patients with a certain degree of clinical response (e.g. no worsening) and absence of use of additional medication. These could be the basis for secondary or primary analyses.

Rank-based analyses could also be possible, where patients are ranked based upon their result on the variable along with their status in terms of specified intercurrent events (e.g. timing of non-investigational symptomatic medication, timing of treatment discontinuation). Such approaches are limited in that they may not provide a useful estimate of the size of the treatment effect, but they could be used to establish the existence of a statistically significant difference between the groups, with estimation following using alternative methods.

Tipping point analyses which explore the extent to which assumptions in respect for imputation or modelling for handling missing data would have to be violated before a positive result is lost could be conducted as sensitivity analyses to show how robust the results are to the handling of missing data.

Whatever choice is made must be prespecified and fully justified in the protocol.

11.2. Additional analyses aimed at demonstrating disease modifying properties of a treatment

Having established and estimated a treatment effect, different considerations for the target of estimation and methods of analysis are likely to apply in order to establish the theoretical nature of a treatment effect, specifically to establish through clinical data a disease modifying effect. This is a supplementary exercise to complement understanding of mechanism of action and longitudinal effects on relevant biomarkers.

An example of this is when the objective is to demonstrate that a treatment is disease modifying (rather than symptomatic), such as analysis of the second stage of a delayed start design. Here experience is extremely limited, and the estimand of interest requires careful reflection, The theoretical property of treatment might be best investigated through an estimand of interest had all patients adhered to treatment. In these situations use of an MMRM type approach to the analysis based on patients from the same treatment group who continue with treatment could be justified, as could other forms of slope analysis. Analyses imputing pessimistic data after withdrawal from randomised treatment, e.g. based on placebo data would not be appropriate for this target of estimation.

For a disease modifying drug seeking approval, a situation could be envisaged where a randomised, placebo-controlled study is first analysed to test for a treatment effect using an estimand as outlined in section 11.1, and then is also analysed using an MMRM type approach to justify that the effect is disease modifying by showing divergent slopes.

12. 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 years 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. The population should reflect the target population regarding age as well as comorbidity.

13. 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 for BACE inhibitors.
After short term trials, on treatment follow up of at least 6months is recommended. This can be achieved with an open label trial extension in patients considered as responders and desiring continuing the treatment. Inaddition 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.

13.1. Neurological adverse events

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 for antibodies targeting fragments of β-amyloid, 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.

13.2. Psychiatric adverse events

Specific attention should be paid to the occurrence of hallucinations and other signs and symptoms of affective or psychotic disorders. Neuro-behavioural abnormalities, particularly disorientation, agitation and aggressive behaviour should be recorded depending on the pharmacodynamic profile of the test drug.

Overdose and suicide

Depending on the mechanism of action, intended treatment regimen, risks and effects of overdose should be studied.

The potential for the test product to precipitate suicidal thoughts and behaviour should be systematically 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;an analysis of any impact relative to dose, duration of treatment and other contributing factors should be evaluated. Narrative summaries of suicidal patient statements or behaviours should be provided.

13.3. Cardiovascular adverse events

Depending on 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.

13.4. 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 maybe 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.
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 arisk 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 the preclinical AD definition 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 plus 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 non-amnestic 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.

Towards a unified conception of preclinical AD (Dubois 2016)

Proposed definition	NIA-AA, 2011	IWG-2, 2014	Proposed criteria, 2016
AD starts			
With the first brain lesion	+		
With the first symptom of AD		+	
When there is evidence of Aß and Tau pathology			+
Preclinical AD can be detected in asymptomatic individuals			
When there is evidence of Aß pathology	+ (stage 1)	+ (PET)	
When there is evidence of Aß and Tau pathology	+ (stage 2)*	+ (CSF)	+
Asymptomatic at risk for AD can be detected in cognitively normal individuals			
When there is evidence of Aß pathology ("Asymptomatic A+") OR evidence of Tau pathology ("Asymptomatic T+")			+

Abbreviations: AD, Alzheimer's disease; NIA-AA, National Institute on Aging/Alzheimer Association; IWG, international working group.
NOTE. The criteria now stipulate that the Aß+ group (A+) is asymptomatic at risk for AD, whereas the Aß+/Tau+ group (A+, T+) is considered as having preclinical AD.
*In the NIA-AA criteria, markers on neurodegeneration (i.e., brain atrophy on MRI or hypo-metabolism on FDG PET) were also considered instead of tau markers to diagnose preclinical AD.

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.

14. References

Albert MS et al.,'The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease', Alzheimers Dement,2011, 7(3): 270-279.

Alzheimer's Association, 'Alzheimer's Association Report – 2014 Alzheimer's disease facts and figures.'Alzheimers Dement, 2014, 10: e47-e92.

Amur S et al., 'Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization.', Clinical pharmacology and therapeutics, 2015, 98(1): 34-46.

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

Bateman RJ et al.,'Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease',N Engl J Med, 2012, 367:795-804.

Bittner T et al., 'Technical performance of a novel, fully automated electrochemiluminiscence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid.',Alzheimers Dement. 2016 May; 12(5):517-26

Blennow K et al.,'Biomarkers in Amyloid-ß Immunotherapy Trials in Alzheimer's Disease.', Neuropsychopharmacology, 2014, 39: 189-201.

Broich K et al.,'Biomarkers in clinical trials for neurodegenerative diseases: Regulatory perspectives and requirements.' Progress in Neurobiology, 2011, 95: 498-500.

Burnham SC et al., 'Novel Statistically-Derived Composite Measures for Assessing the Efficacy of Disease-Modifying Therapies in Prodromal Alzheimer's Disease Trials: An AIBL Study.', Journal of Alzheimer's disease, 2015, 46(4): 1079-89.

Carillo MC et al.,'New and different approaches needed for the design and execution of Alzheimer's clinical trials.', Alzheimers Dement, 2013, 9 (4): 436-437.

Cavedo Eet al.,'The road ahead to cure Alzheimer´s Disease: Development of biological markers and neuroimaging methods for prevention trials across all stages and target populations.', J Prevention Alzheimer's Disease, 2014, Dec; 1(3): 181-202

Cedarbaum JM et al., 'Rationale for use of the Clinical Dementia Rating Sum Boxes as primary outcome measure for Alzheimer´s disease clinical trials.', Alzheimers Dement, 2013, Feb;9(1 Suppl):S45-55.

Chare L et al.,'New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications.', Neurolol Neurosurg Psychiatry, 2014, 85: 866-871.

Coley N et al., 'Suitability of the Clinical Dementia Rating Sum Boxes as single primary endpoint for Alzheimer´s disease trials', Alzheimers Dement, 2011, 7: 602-610.

Cortes-Blanco A et al., 'Florbetapir (18F) for Brain Amyloid Imaging - Highlights on the European marketing Approval', Alzheimers Dement, 2014 pii: S1552-5260(13)02842-2.

Cummings JL,'Alzheimer's disease clinical trials: changing the paradigm.', Curr Psychiatry Rep,2011, 13: 437-442.

de Souza L et al., 'Biological markers of Alzheimer´s disease.', Arq Neuropsiquiatr.,2014, 72: 227-31.

De Strooper B et al., 'The Cellular Phase of Alzheimer's Disease.', 2016, Cell, 164(4): 603-615.

Doody RS et al.,'Phase 3 Trials of Slanezumab for Mild-to:Moderate Alzheimer´s Disease', N Engl J Med, 2014, 370:311-21.

Donohue MC et al.,'The Preclinical Alzheimer Cognitive Composite Measuring Amyloid-Related Decline',JAMA Neurol, 2014, Aug;71(8):961-70.

Dubois B et al., 'Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria.', Alzheimer's & dementia, 2016, 12(3): 292-323.

Dubois B et al.,'Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria.' Lancet Neurol, 2014, 13 (6): 614-629.

Dubois Bet al.,'Revising the definition of Alzheimer's disease: a new lexicon.', Lancet Neurol 2010, 9(11): 1118-1127.

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

Fargo K et al.,'Alzheimer's Association Report – 2014 Alzheimer's disease facts and figures'. Alzheimers Dement, 2014 e47-e97.

Feldman HH et al., 'Alzheimer's disease research and development: a call for a new research roadmap',Ann N Y Acad Sci, 2014, Apr;1313:1-16.

Fleisher AS et al., 'Associations between biomarkers and age in the Presenilin 1 E280A Autosomal Dominant Alzheimer Disease Kindred A Cross-sectional study.', JAMA Neurol, 2015, 72(3): 316-324

Fiandaca MS et al., 'Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: A case-control study.', Alzheimers Dement, 2015,11(6): 600-607.

Genin E et al., 'APOE and Alzheimer disease: a major gene with semi-dominant inheritance.', Molecular Psychiatry, 2011, 16(9): 903-907.

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

Gorno-Tempini ML et al.,'Classification of primay progressive aphasia and its variants.', Neurology, 2011, 76: 106-1014.

Gray JA et al., 'The need for thorough phase II studies in medicines development for Alzheimer´s disease.' Alzheimer´s Research and Therapy, 2015,7:67

Haas C,'Strategies, Development, and Pitfalls of Therapeutic Options for Alzheimer's Disease.', J Alzh Disease, 2012, 28: 241-281.

Haas M et al., 'The European medicines Agency´s strategies to meet the challenges of Alzheimer disease.', Nat Rev Drug Discov, 2015, 14 221-222

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

Hampel H et al.,'Biomarkers for Alzheimer's disease therapeutic trials.', Progress in Neurobiology,2011, 95: 579-593.

Huang Y et al., 'Development of a straightforward and sensitive scale for MCI and early AD clinical trials.', Alzheimers Dement, 2015, Apr;11(4):404-14.

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

Jack CRet al., 'Shapes of trajectories of five major biomarkers of Alzheimer's Disease.', Arch Neurol,2012, 69 (7): 856-867.

Jack CR et al.,'Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers', Lancet Neurol, 2013,12(2):207-16.

Jekel K et al., 'Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review', Alzheimers Res Ther. 2015, Mar 18;7(1):17.

Jellinger KA et al., 'Prevalence of dementia disorders in the oldest-old: an autopsy study.'ActaNeuropathol. 2010; 119: 421-33

Karin A et al., 'Psychometric evaluation of ADAS-Cog and NTB for measuring drug response', Acta Neurol Scand. 2014 Feb;129(2):114-22.

Karran E et al., 'Antiamyloid Therapy for Alzheimer´s Disease – Are We on the Right Road?',N Engl J Med, 2014, 370: 377-378.

Karran E et al.,'A critique of the drug discovery and Phase 3 clinical programs targeting the amyloid hypothesis for Alzheimer Disease.', Ann Neurol, 2014, 76: 185-205.

Karran E and De Strooper B, 'The amyloid cascade hypothesis: are we poised for success or failure?', Journal of Neurochemistry, 2016, 139 Suppl 2: 237-252.

KesterMI et al.,'Serial CSF sampling in Alzheimer's disease: specific versus non-specific markers.' Neurobiol Aging 2011 33 (8): 1591-1598.

Klunk WE,'Amyloid imaging as a biomarker for cerebral ß-amyloidosis and risk prediction for Alzheimer dementia.', Neurobiol Aging,2011, 32 (Suppl. 1): S20-S36.

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

Landau SM et al., 'Comparing PET imaging and CSF measurements of Aß.',AnnNeurol, 2013, Dec;74(6):826-36.

Landau SM et al., 'Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers.', European Journal of nuclear medicine and molecular imaging, 2014, 41(7): 1398-407.

Langbaum JB et al.,'An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease.', Alzheimer´s Dement, 2014, Apr 18. pii: S1552-5260(14)00063-6.

Lim YY et al., 'APOE ε4 moderates amyloid-related memory decline in preclinical Alzheimer's disease.', Neurobiology of aging, 2015, 36(3): 1239-44.

Lim YY at al., 'Sensitivity of composite scores to amyloid burden in preclinical Alzheimer´s disease: Introducing the Z-scores of Attention, Verbal fluency, and Episodic memory for Nondemented older adults composite score.',Alzheimer´s Dement, 2016,2: 19-26

Mackenzie IR et al., 'Nomenclature and nosology for neuropathological subtypes of frontotemporal lobar degeneration: an update',ActaNeuropathol,2010, 119:1-4.

Mangialasche F et al.,'Alzheimer's disease: clinical trials and drug development.', Lancet Neurol, 2010, 9: 702-716 179.

Manolis E et al., 'New pathway for qualification of novel methodologies in the European Medicines Agency.', Proteomics ClinAppl, 2011, 5(5-6): 248-255.

Mapstone M et al., 'Plasma phospholipids identify antecedent memory impairment in older adults',Nat Med., 2014, Apr;20(4):415-8.

McEvoy LK et al., 'Biomarkers for the clinical evaluation of the cognitively impaired elderly: amyloid is not enough', Imaging Med, 2012, 4 (3): 343-357.

McKeith IG et al., 'Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.', Neurology, 2005, Dec 27; 65(12):1863-72.

McKhann G et al., 'Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease.',Neurology, 1984, 34 (7):939-44.

McKhann GM et al., 'Clinical and Pathological Diagnosis of Frontotemporal Dementia.',Arch Neurol,2001, 58: 1803-1809.

McKhannGMet al, 'The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.',Alzheimers Dement, 2011, 7 (3): 263-269.

Medina M et al., 'New perspectives on the role of tau in Alzheimer´s disease. Implications for therapy', BiochemPharmacol. 2014 Apr 15;88(4):540-7.

Mormino EC et al., 'Amyloid and APOE ε4 interact to influence short-term decline in preclinical Alzheimer disease', Neurology, 2014, 82(20): 1760-1767.

Morris G et al., 'Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease', Acta Neuropathol Commun., 2014, Sep 18;2(1):135.

Morris JC et al., 'Recommendations for the incorporation of biomarkers into Alzheimer clinical trials: an overview', Neurobiol aging, 2011, 32: S1-3.

Morris JC et al., 'Developing an international network for Alzheimer research.',ClinInvestig (Lond)., 2012, Oct 1;2(10):975-984.

Morris JCetal., 'Harmonized diagnostic criteria for Alzheimer´s disease: recommendations, J of Int Med,2014, 275: 204-213.

Mullane K et al., 'Alzheimer's therapeutics: continued clinical failures question the validity of the amyloid hypothesis – but what lies beyond?', Biochem Pharmacology, 2013, 85, 289-305

Ngandu T et al., 'A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial', Lancet, 2015, 385: 2255-2263

Neary D et al., 'Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria.',Neurology,1998, 52: 1546-54.

O´Bryant SE et al., 'Guidelines for the standardization of preanalytic variables for blood-based biomarker studies in Alzheimer´s disease.', Alzheimers Dement, 2015, 11: 549-560.

Petersen RC et al.,'Mild cognitive impairment: clinical characterization and outcome.', Arch Neurol, 1999, 56(3):303-8.

Pfeffer RI et al., 'Measurement of functional activities in older adults in the community.', J Gerontol, 1982, 37:323–329.

Querfurth HW et al., 'Alzheimer's disease.', N Engl J Med, 2010, 362(4): 329-344.

Rascovsky K et al., 'Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia.', Brain, 2011, 134:2456-2477.

Reiman EM et al., 'Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments', Alzheimers Dis., 2011, 26(Suppl 3): 321–329.

Reitz C, 'Alzheimer's Disease and the Amyloid Cascade Hypothesis: A critical Review.' ,Int J Alzheimer's Dis, 2012, Epub 2012 Mar 17.

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

Ryman DC et al., 'Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis.', Neurology, 2014, 83(3): 253–260.

Salloway S et al.,'Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer´s Disease.', N Engl J Med, 2014, 370: 322-33.

Sikkes S et al, 'A new informant-based questionnaire for instrumental activities of daily living in dementia', Alzheimers Dement, 2012, 8: 536-543.

Simon, R, 'Biomarker based clinical trial design' Chinese clinical oncology, 2014, 3(3).

Skinner J et al., 'The Alzheimer´s Disease Assessment Scale-cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI', Brain Imaging and Behavior, 2012, 6: 489-501.

Sperling RA et al., 'Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease', Alzheimers Dement, 2011, 7(3): 280-292.

Sperling RA et al., 'Biomarkers of Alzheimer Disease: current and future applications to diagnostic criteria', Continuum, 2013, 19 (2): 325-338.

Storandt M et al., 'Toward a multifactorial model of Alzheimer disease.',Neurobiol Aging, 2012, Oct;33(10):2262-71.

Su Y et al., 'Quantitative Amyloid Imaging in Autosomal Dominant Alzheimer's Disease: Results from the DIAN Study Group.', PLoS One, 2016, 11(3): e0152082.

Toyn JH et al., 'Interpreting Alzheimer's disease clinical trials in light of the effects on amyloid-ß.',Alzheimers Res Ther, 2014 6: 1-12.

Vellas B et al., 'Prevention trials in Alzheimer's disease: an EU-US task force report', ProgNeurobiol, 2011, 95: 594-600.

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

Villemagne VL et al.,'Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer´s disease: a prospective cohort study.', Lancet Neurol, 2013, 12: 357-67.

Villemagne VL e al., 'Tau imaging: early progress and future directions.', Lancet Neurol, 2015, 14: 114-24

Webster S.J. et al.,'Using mice model Alzheimer´s dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models.',Front Genet, 2014, 5: 1-23

Weiner MW et al., 'The Alzheimer's Disease neuroimaging Initiative: a review of papers published since its inception.', Alzheimers Dement, 2013, 9 (5): e111-194.

Wiesmann M et al., 'Vascular aspects of cognitive impairment and dementia.',JCereb Blood Flow Metab., 2013, Nov;33(11):1696-706.

Zetterberg H et al., 'Understanding the cause of sporadic Alzheimer's disease.', Expert Rev. Neurother, 2014, 14: 621-630.

Annex 1

Qualification opinions in AD:

1. 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. 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)