Received Comments to the Draft Guideline (Rev1) for treatment of Alzheimer's disease and other dementias

EWP/EMEA Workshop

Focus on Dementia

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Guideline on Alzheimer's and other Dementias

- The Revision 1 Draft has been published on the EMEA website on July 2007, for 6-month public consultation.
- Today workshop is an initiative of the EWP/CHMP and the EMEA Scientific Secretariat aimed to get direct feed-back from many stakeholders
- This is in the context of several modalities of fruitful exchange, all put in place to concur to sharing advice between regulators, scientific community, patients representatives and developers, while enhancing the transparency of the complex workflow of medicine approval

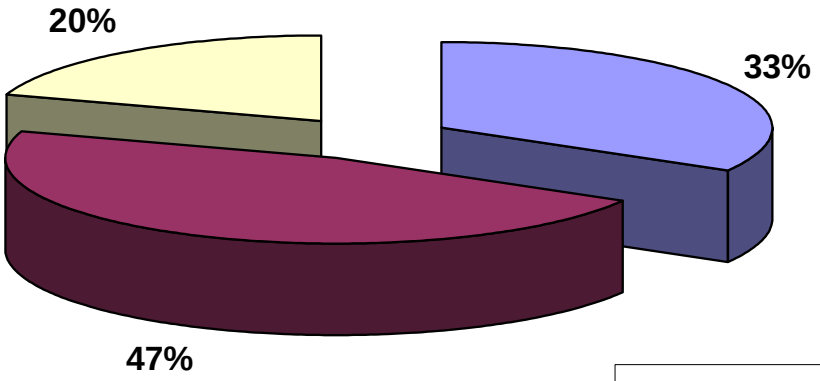
Guideline on Alzheimer's and other Dementias

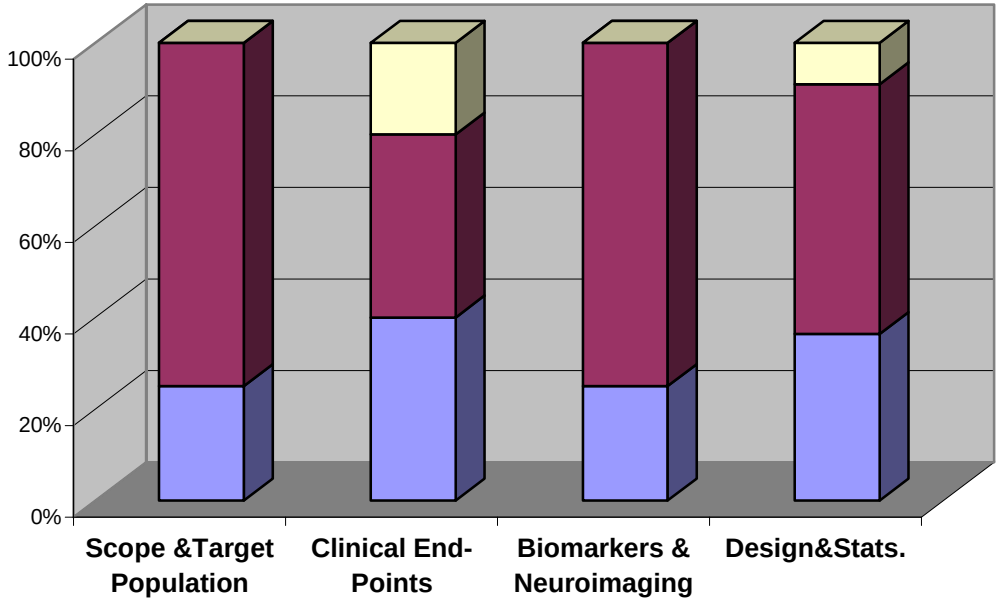
- The scope of the current document encompasses not only Alzheimer's but also other types of dementia, trying to build common basis of regulatory guidance across the therapeutic area of neurodegenerative diseases (a mandatory area according Regulation EC/726/2004).
- The guideline does not deal with the qualification of biomarkers (BM), as it was felt that specific provisions are necessary on this matter.
- The EMEA is currently putting in place a Qualification Process of Innovative Drug Development Methods, to dynamically address the evaluation of BM for a intended use (non-clinical/translational/ therapeutic area related, etc.)

GL Dementia Rev.1; Comments from the Stakeholders

Overview

Comments provided by:





- Academia
- Industry
- CROs/Consultants/Non-Profit Org.

Scope & Target Population (1)

Currently epidemiological and clinical studies are underway to establish validated criteria for definition of "pre-dementia stages". Need for a clear regulatory position on pre-dementia stages of AD	Clarification is needed now for defining some of these early dementia populations, particularly in AD as the current guidelines provide no direction on how this patient population might be appropriately identified for pivotal clinical trials.
The definition of dementia outlined still requires memory impairment. There are dementias where memory impairment is either not significant or not present.	Suggested re-wording "Dementia is a clinical syndrome characterized by acquired deficits in at least two cognitive domains that cannot be better explained by another medical condition. The cognitive impairment may be progressive or static but need to be of sufficient severity to impair occupational or social functions (DSM IV R, ICD10).

Scope & Target Population (2)

Huntington's is mentioned in the Introduction, but not in the scope.	Clarify if Huntington's is outside the scope of the document
To improve diagnostic characterisation of "other dementias"; provide guidance on how to ensure a probable 'pure' AD population in AD trials	As there are limitations of the NINCDS-ADRDA criteria to exclude patients with mixed AD-VaD or other dementia syndromes, exclusion criteria should be employed e.g. clinical history, neuro-imaging. Include acceptable methods for reaching 'probable' separation of 'pure' and 'mixed' forms of dementia in clinical studies.
FTLD prevalence is estimated 3.6-15.0:100.000 and is the second most common cause of dementia in patients younger than 65.	The omission of guidance could delay research in this field. Consider to include specific recommendations for development in frontotemporal dementia.

Scope & Target Population (3)

Dementia is an age related disease: most patients are older than 70 and many are over 85.	PK and PD studies in the oldest old (over 85) are needed; To include at least a sub-group of frail patients with co-morbidities and “polypharmacy”; Patients of this group should undergo a comprehensive geriatric assessment not limiting evaluation to cognitive and functional aspects.
The prevalence of dementia in nursing homes is up to 40-50%.	These patients should not be excluded from clinical trials.

Scope & Target Population(4)

"genetic screen": late onset vs. early onset AD and associated genetic patterns. No distinction is given.	Policy to be clarified	Appropriateness of genetic screening to help with diagnosis/prognostic factors
Subtypes of dementia : To address clinical differences: symptom patterns, differences in progression, etc.	How to characterize dementia subtypes	Comments on the acceptance of a label restricted to subtypes (e.g. Alzheimer's disease)
Non-standard definitions for staging of dementia severity.	To indicate operational standards for staging	Ex: Utility of CDR for clarifying severity of dementia (CDR: 0.5 is questionable dementia; 1 is mild; 3 is moderate; 5 is severe).

Primary End-Points (1)

BPSD (mood changes, irritability, anxiety, delusions, hallucinations, agitation, depression, sleep disturbances, appetite changes, and alterations in sexual behaviors)	Could a 4th domain be considered?	Behavioral symptoms have major impact on patient and caregiver quality of life, accelerate cognitive decline and commonly precipitate placement of the patient in a nursing home. They are more influential than cognitive decline in determining which patients are institutionalized. There is a measurable increase in cost for every 1-point increase in score on the NPI.
"Global" co-primary end- point versus ADL. Demonstration of changes in ADL in 6-month placebo-controlled trials is extremely difficult, especially in mild AD.	Harmonisation with the US-FDA in order to facilitate global CTs.	To specify if the new endpoint requirements apply to drugs with disease-modifying as well as drugs with symptomatic effects.

Primary End-Points (2)

It is important to recognise that ADAS-Cog may not be the best instrument to assess cognition. However the mention of specific rating tools (like NTB) may be taken as an implicit recommendation by the EMEA that trial designers should use this specific battery.	To avoid creating *de facto* standards. Do not restrict the use and the development of other measures.	Remove the reference to specific rating scales by name and instead provide guidance on the criteria for selecting appropriate test-batteries. A number of alternatives tools have been validated and may be used. Every assessment must be adapted and validated for the distinct subtypes and within subtypes the original validated should be used without further adaptations.
The chapter on efficacy measures does not address what a clinically meaningful difference to these endpoints would be, or how clinical meaningfulness could be demonstrated. In order to avoid different views on this important point the agency should give some insight into their thinking.		

Use of Biomarkers (BMs)

"fit-for-purpose use" of BMs in AD CTs	To provide a better definition	1) Biomarker assay/measure has been technically validated (good precision, sensitivity and specificity) 2) The biomarker is compelling related to the pathophysiology of AD 3) The biomarker changes over the course of the disease 4) Changes in the biomarker correlate with clinical benefit associated with effective treatment.
Use of BMs as supportive evidence of disease modification	To define more clearly their use	If a BM meets "guidance defined fit-for-purpose criteria" – then the biomarker "may" be considered as supportive evidence for disease-modification.
Qualification of BMs and 'weight of evidence' approach	Why BM qualification is out of scope?	MRI, CSF Tau/pTau, a-beta are mentioned: to state clearly if these BMs are *qualified* or *validated*.

Study Design & Statistics (1)

'different drugs should be developed directed towards either symptomatic change ***or*** *to modification of aetiological and pathophysiological processes'* is restrictive: some development compounds may have an effect on both the symptoms and the progression of the disease.	Do not exclude a dual response	*……'there will be probably be no single "anti-dementia" drug, but different drugs should be developed directed towards either symptomatic change and/or to modification of aetiological and pathophysiological processes'*
Should a study (investigating both symptomatic effect and DM) follow a hierarchical approach and first establish symptomatic effect then moving to the 2 co-primary for DM?	BMs as co-primary for disease modifying claim?	

Study Design & Statistics (2)

The two-step approach proposed in the guideline for disease modification "is not considered helpful as *even some symptomatic treatments might well delay certain disabilities"*	To describe the clinical programme to support a first-step claim	To discuss the importance or utility of time-to-event analysis (*e.g. time to a 1 point decline of the CDR or time to a 3 point decline on the MMSE or even time to institutionalization)* in obtaining a disease modification claim with some proposed examples . To provide which effect size over background therapy in AD would be considered clinically meaningful on key co-primary endpoints
"Results from appropriate trial designs or analyses can provide evidence of change in the underlying disease process that is convincing as evidence from validated BMs".	*Ad-hoc* designed studies could be sufficient for a full DM claim?	To consider also proof of evidence based on new methods of analysis such as natural history staggered start (NHSS) with or without incorporation of adequately validated BMs.

Study Design & Statistics (3)

"Mandating pure placebo-controlled trials may cause discrimination by fostering research in individuals or regions where access to current therapies is limited".	Methodology for add-on CTs to be developed in the document.	Add-on is recommended for disease-modifying CTs. "Ethic Committees will not allow denying patients the normal standard of care for their stage".
Study duration is a feasibility issue (18-month duration recommended for disease modification).	Study duration?	Patients will meet different stages of disease for which the standard of care implies the start of certain approved treatments. "It seems unrealistic that subjects will not need dose change or new treatment over 18 months"

Study Design & Statistics (4)

"Pure" AD inclusion criteria may limit both recruitment and generalisation to source population.	To ensure generalisability of results	To allow some vascular components in AD trials. To avoid to remove too many subjects due to "fluctuations" during run-in/wash-out phase. Age considerations, etc.
Text includes suggestion for survival analysis as primary analysis and "slope" analysis as secondary. Given the evolving experience in disease modification, this should be updated to a more general statement Currently there are no accepted clinical keystones in disease modification to pre-specify: end-points like institutionalisation, death, etc. will be relatively rare. In addition these end-points may not reflect the true progression of the disease.	For disease modifying CTs: survival versus "slope" analysis	It may be appropriate to conduct both analyses without reference to which would be primary and secondary. Also to specify that alternative approaches are acceptable provided there is adequate justification.
Statistical aspects in the guideline should be expanded and strengthened, e.g. the most appropriate method to account for dropouts in CTs, etc.		

Thank you for your attention.