30 July 2016

Submission of comments on 'Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias ' (EMA/CHMP/539931/2014)

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Several recommendations of the draft guideline are not in agreement with ethical requirement for clinical research in demented patients, such as the WMA Declaration of Helsinki (Fortaleza, 2013) principles 8 (*While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects*), 19 (*All vulnerable groups and individuals should receive specifically considered protection*), and 33 (*patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.*). Therefore Hirnliga e.V., a non-profit organization of clinicians and researcher in the field of dementia, strongly suggest to reduce the mandatory use of placebo or experimental compounds for symptomatic treatment of demented patients to the absolute minimum required for scientific purposes and ethically justified, as stipulated below.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
554-563		Comment: It is not ethically justified to withhold an approved standard of care symptomatic treatment, such as cholinesterase inhibitors, from patients with dementia for research purposes. Current guidelines unambiguously recommend treatment of patients with mild to moderate Alzheimer's dementia (Hort et al. 2010; Ihl et al. 2011; Ihl et al. 2015; Deuschl et al. 2016; NICE 2016). The treatment should start after diagnosis (Ihl et al. 2011). There is evidence from long-term observational and controlled studies that early initiation and persistent exposure to AD therapy lead to delays in nursing home admission and significantly slower rates of cognitive and functional impairment. Analysis of a placebo-controlled trial followed by an open-label continuation trial indicated that treatment delay by one year may reduce benefits as compared with those seen in patients starting donepezil therapy early in the course of Alzheimer's disease (Winblad et al. 2006). Due to the fact that antidementia drug trials need to be of considerable duration, long two-arm trials without placebo would certainly increase the appeal for participants with mild to moderate and severe AD to enroll in such studies. This, in turn, would lead to an enhanced feasibility of antidementia drug trials and thus to a shortened trial-to-practice gap time. Substantial differences between placebo patient populations in the different dementia trials that have been worrisome, would	

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		probably decrease dramatically because phase III trial would be faster and more efficient, due to improved enrollment and thereby a smaller number of different study centers needed. Proposed change: ~~It is acknowledged that the feasibility of long-term placebo controlled monotherapy studies has become seriously limited in mild to moderate and severe AD due to the availability of several symptomatic treatments. However, since substantial differences between placebo patient populations in the different dementia trials have been shown and improvement without treatment cannot be ruled out the preferred design option is still a three-arm study comparing the test product to an already approved treatment and to placebo for assay sensitivity. The active control is needed in order to place the new treatment in the context of other available symptomatic treatment options. In order to minimize the ethical concerns for the use of placebo, a placebo controlled trial in which subjects are permitted to take standard therapy if clinically indicated could be considered, depending on the nature of the new product. Stratification according to baseline background therapy should be undertaken and it would typically be advantageous to include sufficient patients with no baseline background therapy in order to allow for an evaluation of the new product as monotherapy. Alternatively a superiority trial versus active control could be considered.~~ The preferred design option of trials for new symptomatic compounds should	

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		be adapted to the phase of drug development. While in phase IIa/b a placebo comparison appears to be the scientifically appropriate choice, this is debatable for phases III (or even IIb) where a two-arm design without a placebo control seems ethically preferable and scientifically justifiable. Such an approach would ensure that large numbers of participants of phase III clinical trials would not be withheld from active treatment for clinically relevant periods of time. Depending on the nature of the new product, stratification according to baseline background therapy should be undertaken and it would typically be advantageous to include sufficient patients with no baseline background therapy in order to allow for an evaluation of the new product as monotherapy. For phases II a/b, however, the preferred design option is a three-arm study comparing the test product to an already approved treatment and to placebo for assay sensitivity. At this phase, the range of heterogeneous responses can be estimated to be used for proper power calculations for the phase III two-arm trials. The two-arm phase III trial should be conducted in the form of a superiority trial versus active control.	
569		Comment: From the proposed wording it remains unclear, whether 12 month treatment is requested for the randomised double blind phase of pivotal efficacy trials for symptomatic dementia treatment, or for open label safety follow up. For sake of clarity, design of safety trials should only be handled	

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		in section 14. Proposed change (if any): ~~On-treatment follow-up of at least 12 months is recommended (see section 14).~~	
782-783		Comment: Based on neuropathological analyses, at least half of patients have some type of mixed disease (Jellinger 2013). Mixed dementia is an important clinical reality and development of better treatments for mixed dementia represents an important clinical need on its own, not secondary to treatment of "pure" disease. Development of a better treatment effective in a frequent type of mixed dementia would represent an important progress, even if efficacy in pure disease has not been demonstrated. Proposed change (if any): ~~Generally, it is recommended to start the development program in the "pure" disease forms and only thereafter extend the scope of development to the mixed forms.~~	
857-858		Comment: It is not ethically justified to withhold approved standard of care symptomatic treatments, such as cholinesterase inhibitors, from patients with dementia for research purposes (see above). Requesting additional 12 months safety follow-up for new experimental drugs also for symptomatic treatments of dementia will withhold standard treatment from participants for this period. This would happen in a situation, where the benefit of the experimental treatment has not yet been	

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		established. 12 month on treatment safety trials can only be requested, after the efficacy has clearly been established in comparison to approved standard treatments. Proposed change (if any): ~~In short term trials, on treatment follow up of at least 12 months beyond the double blind phase is recommended.~~	

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