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Committee for Medicinal Products for Human (CHMP)

Concept paper on the need for revision of the guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

Agreed by Central Nervous System Working Party (CNSWP)	19 May 2025
Adopted by CHMP for release for consultation	14 July 2025
Start of public consultation	06 August 2025
End of consultation (deadline for comments)	28 February 2026

The proposed guideline will replace 'Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease' (CPMP/EWP/553/95 Rev.2 Corr.1*).

Comments should be provided using this EUSurvey. For any technical issues, please contact the EUSurvey Support

Keywords	Sporadic Alzheimer´s Disease (AD), preclinical and early AD, AD dementia, Biomarkers

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1. Introduction

Dementia represents one of the most devastating healthcare problems faced by Europe and has been recognized as public health priority by the World Health Organization (WHO) since 2017 [1]. Alzheimer´s disease (AD) is by far the most common form, affecting 60 to 80% of the individuals living with dementia [2,3]. Treatment options are still limited and no treatment has been shown to stop the progression of clinical signs and symptoms to date.

Recent advances in the field of AD, including an approval in the EU, and the learnings from several marketing authorisation applications (MAAs) for early AD treatments are the basis for the revision of the guideline on the clinical investigation of medicines for the treatment of AD.

2. Problem statement

The current guideline requires revision to incorporate recent developments in the definition of AD. These changes have important implications for the design and conduct of clinical trials across all stages of sporadic AD.

The ongoing development and validation of plasma biomarkers raises the potential of using biomarkers not only in the research but also in clinical settings to assist the diagnostic work-up of patients with suspected AD [9, 10, 11].

Recently, there has been a proposal to shift conception of AD diagnosis towards a purely biological model [https://aaic.alz.org/nia-aa.asp, 4, 5] and to replace the previous clinical- biological definition [6,7,8]. Biological models of AD, incorporating recent advances in biomarkers, have been proposed as a bridge between research and clinical care, to reflect current science [9]. However, these criteria are not consistent with clinical practice guideline recommendations, this particularly applies to the asymptomatic stage [10].

Additionally, the presence of new treatments is a change in the landscape that raises the question of how to conduct clinical trials, how to define the estimands and how to study potential combination treatments.

Furthermore, the recent experience with MAAs for anti-amyloid treatments, one of which (Leqembi) has now been authorised in the EU, has highlighted the importance of planning for longer term data in terms of both safety and efficacy. With respect to safety adverse events of special interest (AES), safety monitoring and stopping rules need to be defined considering also that safety may differ in subgroups.

Moreover, the development and evaluation of clinical outcome measurement tools that combine clinical meaningfulness and sensitivity to changes in the early stages of AD is an ongoing area of research.

3. Discussion (on the problem statement)

In the proposed update of the guidance document, the following issues will be discussed:

- The evolution of diagnostic criteria, since they have potential implications on both the definition of the target population and on the eligibility criteria for clinical trials;
- The selection of appropriate endpoints, especially for early stages of AD since currently used scales have mostly been developed and validated in later stages of the disease and are not sensitive enough early on;

- Recommendations for trial designs in preclinical asymptomatic AD with the aim of secondary prevention because this is an important treatment goal with huge societal implications, and specific trial methodology considerations apply;
- Recommendations for the context of use of biomarkers, including biomarkers for patient selection (diagnostics and for enrichment), as prognostic or predictive markers, as endpoints, and for monitoring treatment response however clinical endpoints are still needed as long as surrogacy for clinical effects is not established;
- Definition of estimands and trial designs in a setting where amyloid-targeting treatments may be increasingly used for patient management;
- Estimands and trial design considerations for combination treatments;
- Trial design considerations to support treatment paradigms in terms of duration of treatment, rules for treatment discontinuation (e.g. upon progression or upon normalisation of a biomarker) and re-treatments;
- Duration of trial to allow capturing clinical relevant effects ;
- Definition of AESI, safety monitoring and stopping rules.

4. Recommendation

In conclusion, the CNSWP recommends updating the current Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease taking into account the issues identified above.

5. Proposed timetable

It is planned to release for consultation a draft CHMP guidance document not later than Q4 2026.

6. Resource requirements for preparation

The CNSWP will draft the document in collaboration with. the Methodological Working Party (MWP), Scientific Advice Working Party (SAWP) and other relevant WPs and committees.

7. Impact assessment (anticipated)

It is expected that the revised Guideline will be helpful in designing state of the art clinical trials in AD, including early AD, and enhancing drug development in the field.

8. Interested parties

The interested parties in the guidance document include learned societies and academia,e.g.

- European College of Neuropsychopharmacology (ECNP);
- European Academy of Neurology (EAN);
- European Psychiatric Association (EPA);
- European Alzheimer’s Disease Consortium (EADC);
- World Dementia Council (WDC);

- International Society for CNS Clinical Trials and Methodology (ISCTM) and others);
- pharmaceutical industry (e.g. EFPIA and others);
- other regulatory agencies.

9. References to literature, guidelines, etc.

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[11] EU Innovation Network Alzheimer's disease EU-IN Horizon Scanning report, November 2024, https://www.ema.europa.eu/en/documents/report/alzheimers-disease-eu-horizon-scanning-report_en.pdf