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Letter to the Editor

Comment by European Alzheimer's Disease Consortium (EADC) investigators on the negative recommendation of the CHMP on the marketing authorization of donanemab for early Alzheimer' s disease

On March 27th, 2025 the Committee for Medical Product for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the refusal of the marketing authorization of donanemab for the treatment of early Alzheimer disease (AD), while on November 14th 2024 the same committee gave a positive recommendation for lecanemab for the same indication. Lecanemab was fully approved by the European Commission on the 15th of April 2025.

The rationale for the CHMP's opposing recommendation remains unclear. Lecanemab and donanemab are comparable in efficacy. In fact, the donanemab vs. placebo difference at 18 months was 0.67 points on the Clinical Dementia Rating Sum of Boxes (CDR-SB) in the phase 3 clinical study TRAILBLAZER-ALZ 2, while it was 0.45 points in the lecanemab phase 3 study CLARITY-AD [1,2].

The CHMP argued that the risks of taking donanemab would not outweigh its benefit even after restriction to non-carriers of the Apolipoprotein Eε4 (*APOE* ε4) allele, who are at lowest risk of side effects. We acknowledge that the overall Amyloid Related Imaging Abnormality (ARIA) rate in TRAILBLAZER-ALZ 2 was higher than in CLARITY-AD [1,2]. However, given that ARIA are mostly asymptomatic and, if symptomatic, mostly of mild to moderate severity and transient, the very few cases of severe ARIA-E and macrohemorrhages with fatal outcome are the primary safety concerns. Of a total of 557 *APOE* ε4 non-carriers in TRAILBLAZER-ALZ 2, one died of an ARIA-related intracerebral hemorrhage [1]. No further deaths in *APOE* ε4 non-carriers in relation to ARIA have been reported neither in the initial TRAILBLAZER-ALZ study [3], nor in the TRAILBLAZER-ALZ 2 extension study [4], or in the recent TRAILBLAZER-ALZ 6 study [5]. The pooled number of *APOE* ε4 non-carriers exposed to donanemab treatment across these studies is around 840, yielding a percentage of 0.1 % fatal cases (n = 1). This single case had superficial siderosis at baseline [1], which was not an exclusion criterion in TRAILBLAZER-ALZ 2, but should arguably be one in the label of donanemab as it is in the case of lecanemab. Hence, with baseline superficial siderosis and *APOE* ε4 carrier status as exclusion criteria, there would have been most likely no treatment-related death in TRAILBLAZER-ALZ 2 and there was none in any of the other studies of the TRAILBLAZER-ALZ program.

In the TRAILBLAZER-ALZ 6 study, modified titration schemes were tested regarding ARIA frequency. One scheme with a lower starting dose but dose equivalence after three months showed similar pharmacokinetics to the standard dosing scheme of TRAILBLAZER-ALZ 2 in combination with lower ARIA rates in both, *APOE* ε4 non-carriers and *APOE* ε4 carrier [5]. TRAILBLAZER-ALZ 6 was designed without a placebo group so that efficacy against placebo cannot be derived from that study. The modified titration scheme of TRAILBLAZER-ALZ 6 is already used in treatment centers in the United States and is under regulatory review by the United States Food and Drug Administration (FDA) and other regulatory bodies.

In addition, the CHMP concluded that the effect of donanemab on the primary outcome (integrated Alzheimer's Disease Rating Scale, iADRS) was smaller in the *APOE* ε4 non-carrier subgroup than in the total group. In contrast, however, the data reported in the TRAILBLAZER-ALZ 2 supplement show greater efficacy of the donanemab in the *APOE* ε4 non-carrier group [1]. It remains unclear on which analyses the CHMP conclusion is based.

The recommendation against donanemab also does not consider the benefits for patients and care partners related to the lower infusion frequency of donanemab compared with lecanemab (four weekly vs two weekly) and of the stopping rules (after 18 months or earlier after amyloid clearance with donanemab vs. continuous treatment with lecanemab). According to our clinical experience, the benefits for patients and care partners and important aspects in treatment decisions are not solely related to efficacy and safety, but also - to a significant extend - to lower treatment-related burden. Finally, having a choice between treatments not only benefits patients and care partners, but also heath care systems, for example regarding pricing, and it serves the prospective development of treatments in real world care.

In summary, the authors consider the discrepancy between the positive recommendation for lecanemab and the negative recommendation against donanemab arbitrary, not consistent with the scientific evidence, and not to the benefit of patients and care partners. We hope that the CHMP reconsiders this decision and eventually provides a positive opinion in alignment with lecanemab, which may follow the same safety measures, including a Controlled Access Programme (CAP) and a Post Authorization Safety Study (PASS). We are strongly convinced that patients with early AD, care partners and health care systems will benefit from a choice between two alternative treatments with comparable efficacy and safety profiles, but different treatment regimes.

Potential conflicts of interest of individual authors regarding drug development in AD are detailed in the statement below.

Statement on AI

Generative AI or AI-assisted technology were not used in the preparation of this manuscript.

Declaration of competing interest

Frank Jessen: FJ has received grants from Roche Pharma and Roche Diagnostics; FJ has received consulting fees from Eli Lilly and Eisai; FJ has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Eli Lilly and Eisai; FJ has received payment for expert testimony from Eli Lilly and Eisai; FJ is Chairman of the EADC.

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WF is member of the steering committee of PAVE, and Think Brain Health. WF is chair of the Scientific Leadership Group of InRAD. WF was associate editor of Alzheimer, Research & Therapy in 2020/2021. WF is associate editor at Brain. WF is member of Supervisory Board (Raad van Toezicht) Trimbos Instituut.

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