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Refusal of the marketing authorisation for Aduhelm (aducanumab) EMA/750220/2021; EMEA/H/C/005558

Dear Dr. Enzmann,

I am writing to you in your function as CHMP Chair and in connection with the refusal of the marketing authorization for Aduhelm (aducanumab) by the EMA (EMA/750220/2021; EMEA/H/C/005558).

I have the following strong scientific and ethical objections at the rejection of ADUHELM by the EMA: In the United States, the FDA indicated ADUHELM for the treatment of patients with mild cognitive impairment (MCI) or mild stages of Alzheimer's disease (AD). With the refusal of marketing authorization for ADUHELM, the EMA refuses the treatment of the 360-420 thousand patients with MCI or mild AD in Germany. For the EU, this number translates into 1.9-2.3 million patients. Given the rapid progression towards more advanced dementia, the longer we wait, the more people will lose their self-determination, one of the highest human rights. Although, the EMA admits that ADUHELM reduces amyloid beta in the brain (parenchymal and vascular amyloid beta) which demonstrates target engagement, strong concerns are raised in regard to safety issues (brain swelling or bleeding, summarized as ARIAs) and a missing link between amyloid reduction and clinical improvements. First, the safety issues apply to all monoclonal antibodies currently under clinical investigation that target and reduce amyloid beta. This is not surprising since almost all AD patients have at least four times more (w/w) vascular amyloid than parenchymal amyloid (amyloid plaques). The safety argument is not convincing since safe treatment with these monoclonals is a matter of titration and careful monitoring of the patient's reaction during the initial therapeutic phase. The statement, that properly monitoring of ARIAs is not possible in clinical practice, is speculation. Second, given target engagement of ADUHELM, the conflicting data regarding clinical improvement should be overcome with Phase 4 studies as requested by the FDA. Therefore, refusal of marketing authorization for ADUHELM is not the appropriate decision.

Considering these scientific and ethical arguments, I strongly suggest to reconsider the refusal of ADUHELM and to change your recommendation into positive opinion.

Best regards,

Konrad Beyreuther
Seniorprofessor distinctus Director
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