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General review

High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 1: Meta-analysis and review of efficacy and safety data, and medico-economical aspects

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ABSTRACT

In 2021, aducanumab, an immunotherapy targeting amyloid-β, was approved for Alzheimer's disease (AD) by the US Food and Drug Administration thanks to positive results on a putative biological surrogate marker. This approval has raised an unprecedented controversy. It was followed by a refusal of the European Medicine Agency, which does not allow the marketing of drugs solely on biological arguments and raised safety issues, and important US coverage limitations by the Centers for Medicare & Medicaid Services. Two other anti-amyloid immunotherapies showed significant results regarding a clinical outcome in phase 2 trials, and five drugs are being studied in phase 3 trials. Compared to those tested in previous trials of the 2010s, the common feature and novelty of these anti-amyloid immunotherapies is their ability to induce a high clearance of amyloid load, as measured with positron emission tomography, in the brain of early-stage biomarker-proven AD patients. Here, we review the available evidence regarding efficacy and safety data and medico-economical aspects for high-clearance anti-amyloid immunotherapies. We also perform frequentist and Bayesian meta-analyses of the clinical efficacy and safety of the highest dose groups from the two aducanumab phase 3 trials and the donanemab and lecanemab phase 2 trials. When pooled together, the data from high-clearance anti-amyloid immunotherapies trials confirm a statistically significant clinical effect of these drugs on cognitive decline after 18 months (difference in cognitive decline measured with CDR-SB after 18 months between the high dose immunotherapy groups vs. placebo = −0.24 points; $P = 0.04$, frequentist random-effect model), with results on ADAS-Cog being the most statistically robust. However, this effect remains below the previously established minimal clinically relevant values. In parallel, the drugs significantly increased the occurrence of amyloid-related imaging abnormalities-edema (ARIA-E: risk ratio = 13.39; $P < 0.0001$), ARIA-hemorrhage (risk ratio = 2.78; $P = 0.0002$), and symptomatic and serious ARIA (7/1321 = 0.53%

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in the high dose groups versus 0/1446 in the placebo groups; risk ratio = 6.44; P = 0.04). The risk/benefit ratio of high-clearance immunotherapies in early AD is so far questionable after 18 months. Identifying subgroups of better responders, the perspective of combination therapies, and a longer follow-up may help improve their clinical relevance. Finally, the preliminary evidence from medico-economical analyses seems to indicate that the current cost of aducanumab in the US is not in reasonable alignment with its clinical benefits.

France

1. Introduction

On June 7th 2021, the US official governmental drug agency (Food and Drug Administration – FDA) approved a potential disease-modifying therapy, aducanumab, to treat Alzheimer's disease (AD). On the contrary, on December 16th 2021, the European Medicines Agency (EMA) rejected the aducanumab application for a standard approval, and Biogen® withdrew its appeal against the EMA decision on April 2022. The Centers for Medicare & Medicaid Services (CMS) decided to severely restrict the drug coverage in the US in April 2022. Despite the controversy around aducanumab's approval, the recent positive results of the phase 2 trials regarding other high-clearance anti-amyloid antibodies, lecanemab, and donanemab, suggest that demonstration of clinical efficacy followed by approval for high-clearance anti-amyloid immunotherapy is highly probable in the upcoming five years. If it happens, such approval will be a game-changer in the management of AD patients and for the organization of memory clinics in France, from the diagnosis and the use of biomarkers to the monitoring and follow-up of these treatments.

This article aims to review the current evidence regarding the biological and clinical efficiency of the high-clearance anti-amyloid immunotherapies closest to approval, summarize the elements of the debate regarding the assessment of aducanumab by the governmental agencies, and make propositions in the case of an upcoming approval of a high-clearance anti-amyloid immunotherapy for its implementation in the French healthcare system. The first part is a review of the literature regarding the efficacy and safety of these drugs, supported by a meta-analysis of the different trials. The second part will discuss different scenarios and make propositions for implementation in France.

2. Aducanumab: where does it come from? Where does it go?

Aducanumab (a.k.a. BIIB037) is a fully human IgG1 monoclonal antibody against a conformational epitope on the amyloid-beta (Aβ) peptide. It was originally identified and cloned by the biotech company Neurimmune® after investigating a cohort of 265 research volunteers in their seventies who were cognitively stable for three years, or recovered from a non-AD mild cognitive impairment, or whose AD barely progressed [1]. It proved to bind to fibrillar Aβ with high selectivity and subnanomolar affinities and soluble Aβ oligomers but not Aβ monomers [2,3]. Neurimmune® started a collaboration and a license agreement with Biogen® in 2007 for aducanumab development and commercialization (it is now co-developed with Eisai®). A phase I trial started in 2011 and monitored after 24 weeks the occurrence of amyloid-related imaging abnormalities (ARIA; [4]) in a single-ascending-dose trial of 0.3 mg/kg to 60 mg/kg intravenous aducanumab in 53 people with mild to moderate AD. The drug was considered safe until the 30 mg/kg dose, with only the three patients who received a 60 mg/kg dose who developed serious adverse events (SAEs) of symptomatic ARIA (which completely resolved by weeks 8–15) [5].

In 2012, Biogen® started a phase Ib trial (PRIME), a randomized, double-blind, placebo-controlled study, which aimed to investigate further, aducanumab safety and tolerability at 1, 3, 6, and 10 mg/kg as well as a titration protocol (monthly infusion) for 12 months; a secondary aim was to test the effect of the drug on amyloid positron emission tomography (PET). This trial went beyond any expectation: first, it proved to be relatively safe and acceptable (there was a higher rate of ARIA as compared to other anti-amyloid drugs tested so far [47% at the 10 mg/kg dose], but in all cases, ARIA was either asymptomatic or fully reversible after treatment discontinuation). Second, it showed the highest rate of amyloid clearance (as measured with amyloid PET) observed so far in patients under anti-amyloid therapies. Third, it showed a significant slowing of cognitive decline on several cognitive scales in a relatively dose-dependent manner [3,6].

Two identically designed, randomized, double-blind, placebo-controlled phase 3 trials (ENGAGE and EMERGE) were subsequently launched in 2015. These trials were performed worldwide with inclusion criteria limiting the severity of AD to patients with mild cognitive impairment (MCI) due to AD or mild AD dementia [7,8], Mini-Mental State Examination (MMSE) score $\geq$ 24/30, Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB) score = 0.5 and a positive amyloid PET scan (visual read). These two trials were designed to reduce the rates of ARIA: 1) using a titration strategy which proved to reduce the ARIA rate from 47 to 35%; 2) excluding patients with high-risk factors of ARIA (see below; [9,10]), and 3) giving a lower dose to APOE ε4 carriers (homozygous or heterozygous, at high-risk of ARIA). These studies aimed to compare the clinical efficacy of low (3 mg/kg in APOE ε4 carriers or 6 mg/kg in non-carriers) or high (initially 6 mg/kg in APOE ε4 carriers or 10 mg/kg in non-carriers) monthly doses of *aducanumab* over 78 weeks with placebo. The primary endpoint was a change in CDR-SB from baseline at week 78, and secondary endpoints were changes in the MMSE score, the 13-item Alzheimer's Disease–Cognitive Subscale (ADAS-Cog 13) score, and the

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Alzheimer's Disease Cooperative Study – Activities of Daily Living – MCI (ADCS-ADL-MCI) score. In 2017, after the report of final ARIA data from the phase Ib trial, an amendment was made to increase the high dose from 6 mg/kg to 10 mg/kg in APOE ε4 carriers. An earlier amendment of the protocols had also changed dose management following ARIA. After resolving mild-to-moderate symptomatic ARIA, participants resumed treatment at the same dose and continued titration to the target dose instead of suspending dosing or resuming at a lower dose. A pooled futility analysis was planned in the trials' design and performed on half of the dataset (data collected up to December 26th 2018, when about half of the participants had completed 78 weeks of treatment). Its negative result led to a premature ending of both ENGAGE and EMERGE trials in March 2019. In October 2019, Biogen® issued a press release to communicate the results of the analysis of the complete dataset (i.e., including the additional patients who could complete the trial between December and March in a new intention-to-treat analysis). These results appeared to be positive regarding the primary endpoint of EMERGE study for the high-dose group but not for the high-dose group of ENGAGE study and not for the low-dose groups of the two trials (see Table 1 for details). These data were finally published in March 2022 in *The Journal of Prevention of Alzheimer's Disease* [11]. The safety data were separately published in November 2021 in the Journal of the American Medical Association (JAMA) Neurology [12]. They highlighted 41.3% of ARIA occurrence in the 10 mg/kg group from the pooled ENGAGE and EMERGE trials (vs. 10.3% in the placebo group) [12]. Several academic research groups re-analyzed the ENGAGE and EMERGE trials using a Bayesian statistical approach and simulated clinical data [13,14]. Thus, the data of the ENGAGE trial were 14-51 times more likely to occur under the null hypothesis (H_0) of absence, rather than the alternative hypothesis (H_1) of the presence of a treatment effect (Bayes Factor $[BF]_{01}$ = 14–51). In contrast, the data of the EMERGE study were 1.3–1.5 times more likely under the alternative hypothesis of presence than the null hypothesis of the absence of the treatment effect (BF_{10} = 1.3–1.5). Even after excluding the rapid progressors, as proposed by Biogen® in their re-analysis of data, the BF values remained comparable: BF_{01} = 42 for the ENGAGE trial and BF_{10} = 3.7 for the EMERGE trial [13]. In other words, it seems more likely that ENGAGE is a ''true'' negative trial than EMERGE is a ''true'' positive trial.

Besides the clinical data, aducanumab proved remarkably efficient regarding amyloid clearance on amyloid PET since a loss of 60.8 centiloid units was observed in the high-dose group of the EMERGE study and 54.0 in the high-dose group of the ENGAGE study. The centiloid scale is a standardized PET-based amyloid load measurement that aims to homogenize amyloid load measurements across tracers and sites. Zero is the average value in ''high certainty'' amyloid-negative subjects (i.e., young subjects), and 100 is the average value in ''typical'' AD patients with dementia [16]. The usual cut-off to define ''amyloid-positive'' and ''amyloid-negative'' individuals is around 10–25 centiloids [17]. This clearance, as measured with amyloid PET, does not seem to be an artifact related to the antibodies themselves, since a case report of autopsy data from a patient under aducanumab confirms this clearance [18].

After discussion with the FDA, Biogen® submitted a Biologics License Application (BLA) on July 7th 2020, for regulatory approval to market. However, on November 6th 2020, when considering the following question: ''In light of the

Table 1 – Results from the phase 3 aducanumab (ENGAGE and EMERGE trials) and the phase 2 donanemab and lecanemab (high dose = 10 mg/kg biweekly; low dose = 10 mg/kg monthly) trials. The sample sizes reflect the patients included in the trials. Adapted from [15].

			Change from baseline at 18 months			Difference from placebo (%)	
Drug	Trial	Clinical scale	Placebo	Low-dose	High-dose	Low-dose	High-dose
Aducanumab	ENGAGE trial		*n* = 548	*n* = 543	*n* = 547		
		CDR-SB	1.56	1.38	1.59	−0.18 (−12%); P = 0.2250*	0.03 (2%); P = 0.8330*
		MMSE	−3.5	−3.3	−3.6	0.2 (−6%); P = 0.4795	−0.1 (3%); P = 0.8106
		ADAS-Cog 13	5.14	4.56	4.55	−0.58 (−11%); P = 0.2536	−0.59 (−11%); P = 0.2578
		ADCS-ADL-MCI	−3.8	−3.1	−3.1	0.7 (−18%); P = 0.1225	0.7 (−18%); P = 0.1506
	EMERGE trial		*n* = 545	*n* = 547	*n* = 555		
		CDR-SB	1.74	1.47	1.35	−0.26 (−15%); P = 0.0901*	−0.39 (−22%); P = 0.0120*
		MMSE	−3.3	−3.3	−2.7	−0.1 (3%); P = 0.7578	0.6 (−18%); P = 0.0493
		ADAS-Cog 13	5.16	4.46	3.76	−0.70 (−14%); P = 0.1962	−1.40 (−27%); P = 0.0097
		ADCS-ADL-MCI	−4.3	−3.5	−2.5	0.7 (−16%); P = 0.1515	1.7 (−40%); P = 0.0006
Donanemab	TRAILBLAZER-ALZ trial		*n* = 126	NA	*n* = 131		
		iADRS	−10.06	NA	−6.86	NA	3.20 (32%); P = 0.04*
		CDR-SB	1.58	NA	1.22	NA	−0.36 (−23%); P > 0.05
		MMSE	−2.98	NA	−2.35	NA	0.64 (−21%); P > 0.05
		ADAS-Cog 13	4.77	NA	2.91	NA	−1.86 (−39%); P < 0.05
		ADCS-iADL	−5.20	NA	−3.98	NA	1.21 (−23%); P > 0.05
Lecanemab	BAN2401-G000-201 trial		*n* = 238	*n* = 246	*n* = 152		
		ADCOMS	0.19	0.17	0.14	−0.03 (−15%); P = 0.228	−0.06 (−30%);P = 0.034
		CDR-SB	1.50	1.24	1.10	−0.25 (−17%); P = 0.255	−0.40 (−26%); P = 0.125
		ADAS-Cog 14	4.90	4.62	2.59	−0.28 (−6%); P = 0.736	−2.31 (−47%); P = 0.017

* primary endpoint.

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understanding provided by the exploratory analyses of Study 301 [ENGAGE study] and Study 302 [EMERGE study], along with the results of Study 103 [PRIME study] and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of the effectiveness of aducanumab for the treatment of Alzheimer's disease?'', among 11 members of the FDA Peripheral and Central Nervous System Drugs Advisory Committee, ten answered ''No'' and one answered ''Uncertain''. This negative opinion was based on the contradictions highlighted by the FDA statisticians [19]. Eventually, on June 7th 2021, the FDA decided to use the ''Accelerated Approval'' pathway to approve the drug, considering that ''although the Aduhelm™ [aducanumab's commercial name in the US] data are complicated with respect to its clinical benefits, FDA has determined that there is substantial evidence that Aduhelm™ reduces Aβ plaques in the brain and that the reduction in these plaques is reasonably likely to predict important benefits to patients'' [20]. Therefore, it was considered legitimate to use the ''Accelerated approval'' pathway under which the FDA approves a drug for a serious or life-threatening illness that may provide meaningful therapeutic benefit over existing treatments when the drug is shown to affect a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. This pathway is usually used to speed up the use of drugs in oncology or, more recently, during the COVID-19 pandemic. It is conditioned to a new trial that will prove the drug's clinical efficacy, which must be completed in the next nine years. Biogen® has recently submitted the final protocol to the FDA for the aducanumab confirmatory study. It is a global placebo-controlled clinical trial that started in June 2022 (ENVISION trial). Biogen® aims to include 1,300 participants with early AD who will take the drug for 18–24 months. The company expects results by 2026 [21,22]. In parallel, the company has also started an open-label trial EMBARK for participants who had been in the ENGAGE or EMERGE trials. These individuals had been off study medication for nearly two years before they were invited to join EMBARK and receive open-label high dose aducanumab. This trial aims to assess the long-term safety of aducanumab in AD. Despite FDA approval, the US commercialization has been severely hampered by the CMS decision to restrict the drug coverage in April 2022 (see below). In March 2022, Eisai® turned over the majority of rights to aducanumab to Biogen® [23].

In December 2021, the EMA recommended the refusal of the marketing authorization for aducanumab in Europe [24]. The agency's refusal relied on three principal arguments: 1) although aducanumab reduces Aβ in the brain, the link between this effect and clinical improvement has not been established; 2) results from the pivotal studies were conflicting and did not show overall that aducanumab was effective; 3) the studies did not show that the medicine was sufficiently safe regarding ARIA, which could potentially cause harm. Furthermore, it was unclear whether ARIAs can be adequately monitored and managed in clinical practice. Biogen® appealed this decision. A re-examination by the Committee for Medicinal Products for Human Use (CHMP) indicated that the data provided thus far would not be sufficient to support a positive opinion on the marketing authorization. Finally, Biogen® withdrew its appeal against the EMA refusal in April 2022. Contrary to the FDA, there is no dedicated application pathway based only on biomarker efficacy. Only the agency can decide whether a drug can obtain full approval or Conditional Marketing Approval (CMA). The granting of a CMA can be based on a surrogate endpoint that shows that the benefits outweigh the uncertainties in the extent of the clinical benefit it translates to, and when confirmation on the clinical benefits is still required, for an unmet medical need for a seriously debilitating or life-threatening disease [25].

2.1. *Donanemab, lecanemab, and high-dose gantenerumab: other candidates for a future approval*

Besides aducanumab, in 2021, two other anti-amyloid immunotherapies phase 2 trials (donanemab and lecanemab) with a high amyloid clearance and a positive (significant) result regarding a clinical outcome were published.

Donanemab (a.k.a. LY3002813) is a humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a and developed and commercialized by Eli Lilly®. It recognizes Aβ (p3-42), a pyroglutamate form of Aβ that is aggregated in amyloid plaques. The donanemab phase 2 study was launched in December 2017 to evaluate the safety, tolerability, and efficacy of an 18-month course of donanemab (initially alone and in combination with Eli Lilly®'s BACE inhibitor LY3202626: this last arm was discontinued in October 2018). Results were published in the *New England Journal of Medicine* in March 2021 [26]. It enrolled 375 participants with MCI or prodromal AD, MMSE scores between 20 and 28, who performed below a cut-off score on the CogState Brief Battery, and who had both a positive amyloid PET scan (florbetapir SUVR $\geq$ 1.17, equivalent to 37 centiloids) and an intermediate level of cerebral tau load measured with tau PET scan (flortaucipir – between 1.15 and 1.46 SUVR). The earliest and latest stages of the disease are theoretically excluded within this range of tau pathology load as measured with PET. Thus, it allows selecting disease stages where an anti-amyloid therapy is supposedly efficient, and a noticeable cognitive decline is expected to be measurable after an 18-month follow-up. The primary outcome was a change in the integrated Alzheimer's Disease Rating Scale (iADRS), a combined cognitive/functional measure for early-stage AD developed by Eli Lilly® [27]. Secondary measures included the ADAS-Cog13, CDR-SB, MMSE, ADCS-iADL, amyloid and tau PET, and volumetric MRI. The intervention consisted of donanemab (700 mg for the first three doses and 1400 mg after that) or placebo, administered intravenously every four weeks for up to 72 weeks. In participants under donanemab treatment, the dose was lowered to 700 mg if the amyloid plaque level assessed by florbetapir PET (performed at 24 and 52 weeks) decreased between 25 and 11 centiloids (indicating removal of amyloid plaques under the pathological cut-off). If the amyloid plaque level was less than 11 centiloids on any single scan or was between 25 and 11 centiloids on two consecutive scans, donanemab was switched to placebo. 257 patients were enrolled: 131 were assigned to receive donanemab and 126 placebo. The baseline iADRS score was 106 in both groups. The change from baseline in the iADRS score at 76 weeks was

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−6.86 with donanemab and −10.06 with placebo (statistically significant difference – see Table 1). Most secondary outcomes showed no substantial difference (Table 1). When comparing donanemab to placebo groups at week 76, the amyloid plaque level and the global tau load were −85.06 centiloids (significant) and −0.01 SUVR (not significant), respectively. ARIA (mainly asymptomatic) occurred with donanemab (38.9% in the donanemab arm vs. 8.0% in the placebo arm). In October 2020, Eli Lilly® began recruiting for TRAILBLAZER-ALZ 2, initially a phase 2 safety and efficacy trial in 500 people with early AD. Inclusion criteria were similar to TRAILBLAZER-ALZ. Participants receive donanemab or placebo, with the primary endpoint being a change in CDR-SB after 18 months. Secondary measures include the MMSE, ADAS-Cog13, iADRS, and ADCS-iADL, amyloid and tau PET, and volumetric MRI, plus pharmacokinetics and measurements of anti-donanemab antibodies. The trial is set to run through mid-2023 at 87 sites in the U.S., Canada, Japan, The Netherlands, and Poland. Since then, Eli Lilly® has enlarged TRAILBLAZER-ALZ 2 to become a phase 3 registration study with 1,500 participants. The ongoing study has already enrolled some people with tau-PET above 1.46 SUVR, but primary efficacy will be determined in 1,000 people who are below this cut-off. The primary outcome is the iADRS, and effectiveness will be judged using a disease-progression model rather than solely on change at the final time point. Results are expected in mid-2023. In June 2021, the FDA granted donanemab "Breakthrough Therapy" designation to speed development and review. In October 2021, Eli Lilly® announced the submission of a licensing application under the same accelerated approval pathway used for aducanumab, based on the TRAILBLAZER-ALZ trial data [28,29]. In January 2022, after that the CMS disclosed a proposed decision memo for a restricted coverage of FDA-approved anti-amyloid immunotherapies (see below), Eli Lilly® announced to defer its timeline to complete the application for accelerated approval [30]. In April 2022, after the CMS final decision memo, the company said it intends to complete its current rolling application for accelerated FDA approval of donanemab this year [31]. Further developments regarding donanemab aim to directly compare aducanumab and donanemab efficacy on brain amyloid clearance in early symptomatic AD (TRAILBLAZER-ALZ4 trial) and its clinical efficacy in delaying the occurrence of cognitive symptoms in asymptomatic-at-risk individuals for AD (TRAILBLAZER-ALZ3 trial). Finally, Eli Lilly® is also developing another monoclonal antibody targeting Aβ (p3-42) and inducing a high clearance of amyloid load, remternetug (a.k.a. LY3372993) [32]. Its phase 3 trial (TRAILRUNNER-ALZ1), with a comparable design to the TRAILBLAZER-ALZ2 trial, started in August 2022.

Lecanemab (a.k.a. BAN2401) is the humanized IgG1 version of the mouse monoclonal antibody mAb158 that binds to soluble Aβ aggregates (oligomers and protofibrils) with high selectivity over monomer and insoluble fibrils. The therapeutic antibody was initially developed at the biotech company BioArtic Neuroscience®. Lecanemab was licensed to Eisai® which, in March 2014, signed a collaboration agreement with Biogen® for joint development. The phase 2 study of lecanemab (BAN2401-G000-201) started at the end of 2012. It was an 18-month US trial that tested five different intravenous doses (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly) in a Bayesian adaptative design: allocation of subsequent enrollees to different groups was adjusted in response to frequent interim analyses [33]. It enrolled 854 people with either MCI due to AD or probable AD dementia with MMSE $>$ 22 and a positive biomarker for brain amyloid pathology (amyloid PET – visual read or CSF). As primary outcomes, the trial measured a 12-month change from baseline in the new Alzheimer's Disease Composite Score (ADCOMS), a composite of cognitive tests [34], and safety. The Bayesian primary endpoint was a predefined 80% posterior probability of being better than placebo by 25% on ADCOMS after 12 months. The dose selection for this unique statistical comparison regarding the primary endpoint was the effective dose 90% (ED90 – defined as the simplest dose that achieves $\geq$ 90% of the treatment effect achieved by the maximum effective dose. The simplest dose is defined as the smallest dose with the lowest frequency of administration). The trial results were published in *Alzheimer's Research & Therapy* in April 2021 [26]. A total of 854 subjects were randomized (placebo, 245; lecanemab, 609, including 152 lecanemab 10 mg/kg biweekly). At 12 months, the lecanemab 10 mg/kg biweekly dose was identified as the target ED90 dose. The 10 mg/kg biweekly dose showed a 64% probability of being better than placebo by 25% on ADCOMS, which missed the 80% threshold for the primary endpoint. At 18 months, 10 mg/kg biweekly lecanemab reduced brain amyloid load (−0.306 SUVR units, equivalent to ∼70 centiloid units) while showing a drug-placebo difference in favor of active treatment by 27% and 30% (significant) on ADCOMS, 56%, and 47% on ADAS-Cog14, and 33% and 26% on CDR-SB versus placebo according to Bayesian and frequentist analyses, respectively (see Table 1 for details). Results regarding CSF biomarkers were supportive of a target engagement (increase in CSF Aβ42 and decrease in p-tau relative to placebo, whereas inconsistent results were noted at 12 months and 18 months for total tau). Lecanemab was well-tolerated with a 12.4% incidence of ARIAs at 10 mg/kg biweekly (5.7% in the placebo group). Cognitive data from the small open-label extension of the lecanemab phase 2 trial indicated that patients who had received treatment still maintained their edge over those initially in the placebo group. The plasma ratio of Aβ42/40 gradually fell during the gap between the blinded and open-label trials – indicating a rise in brain amyloid deposition – but rebounded when open-label treatment resumed. Together, these findings hint at a disease-modifying effect [35]. In March 2019, Eisai began a phase 3 trial called Clarity AD, currently running at 250 sites worldwide. It aims to enroll 1,566 people with early symptomatic AD who receive a 10 mg/kg drug or placebo every two weeks for 18 months, followed by a two-year open-label extension. The primary outcome in the core study is a change in CDR-SB at 18 months, with secondary outcomes of brain amyloid, ADCOMS, and ADAS-Cog14 subscale. CSF biomarkers and amyloid and tau PET will be assessed in optional longitudinal substudies. By March 2021, the company announced that it had exceeded its enrollment goal at 1,794 patients. The readout of this trial will occur in Fall 2022 [36]. In June 2021, the FDA designated lecanemab as a breakthrough therapy, and, in September 2021, Eisai submitted a licensing application under the accelerated approval pathway and did not withdraw it

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after the CMS decision to limit coverage [36,37]. On July 5th 2022, the FDA formally accepted the companies' Biologics BLA for lecanemab, granting it priority review. This means the agency will make a final decision by January 6, 2023. The company has also started, in parallel, a phase 3 trial in asymptomatic-at-risk individuals for AD that aims to test the efficacy of lecanemab in delaying the occurrence of cognitive symptoms (AHEAD 3-45 trial).

Gantenerumab (a.k.a. RO4909832) is a fully human IgG1 antibody designed to bind with subnanomolar affinity to a conformational epitope on Aβ fibril. It is developed and commercialized by Roche® and its US affiliate Genentech®. Two low-dose (105 or 225 mg subcutaneous gantenerumab monthly) phase 2/3 (SCarlet RoAD) and phase 3 (Marguerite RoAD) trials of gantenerumab have failed an interim futility analysis and were prematurely stopped in 2014 and 2016. Low-dose gantenerumab was also one of the two anti-amyloid immunotherapies involved in the DIAN-TU trial, aiming to test anti-amyloid immunotherapy's efficacy in asymptomatic or early symptomatic autosomal dominant AD, which turned out to be negative on clinical outcomes [38]. The Scarlet and Marguerite RoAD trials were switched to an open-label extension study, with participants titrated up to 1,200 mg gantenerumab monthly. Results from this open-label study showed that three years of high-dose gantenerumab in the SCarlet and Marguerite RoAD extension studies lowered brain amyloid by an average of 59 centiloids on florbetapir PET. About one-third of participants in the extension studies developed ARIA-E, the majority were asymptomatic [39]. In a subsequent paper, the company reported continued amyloid reductions in the third year of the extension. Of 30 participants with three-year PET scans, 80 percent reduced their amyloid load below the positivity threshold [40]. In June 2018, Roche® started two new phase 3 trials for prodromal or mild amyloid-confirmed AD with high-dose subcutaneous gantenerumab (GRADUATE 1 and 2), each at 216 different sites worldwide, with a goal of 760 participants each. Participants are titrated up to 1,020 mg gantenerumab or placebo monthly and treated for 24 months, with an option to continue on open-label. The primary endpoint is a change in the CDR-SB. In March 2020, target enrollment for each trial was increased to 1,016. The trials are slated to run till Fall 2022. In October 2021, gantenerumab was granted FDA Breakthrough Therapy Designation, thus expediting its regulatory review [41]. However, in February 2022, after the provisional CMS decision memo release, the company finally decided to wait for the completion of the two phase 3 trials before applying for an FDA approval [42]. The company has also started a phase 2 trial to test the efficacy of a lower but more frequent dose of gantenerumab (weekly 255 mg infusion) as in the same population of patients in the GRADUATE 1 and 2 trials (GRADUATION trial); and a phase 1b/2a multiple ascending dose trial of RO7126209 (a.k.a. RG6102), a new version of gantenerumab engineered to more easily cross the blood-brain barrier using Roche®'s ''brain shuttle'' technology (BRAINSHUTTLE AD trial). This brain shuttle gantenerumab comprises a fragment antigen-binding that binds the human transferrin receptor, and is attached to the gantenerumab effector (Fc) domain. RO7126209 circulating in the bloodstream binds the transferrin receptor on the endothelial cells that make up the blood-brain barrier. This leads to its endocytosis and release into the brain parenchyma. Finally, the company started a phase 3 trial in asymptomatic-at-risk individuals for AD that aims to test the efficacy of gantenerumab in delaying the occurrence of cognitive symptoms (SKYLINE trial).

2.2. *Clinical efficacy and safety: comparison and meta-analysis of high-clearance anti-amyloid immunotherapies*

As a whole, there are currently five anti-amyloid immunotherapies in the latest stages of development with a strong demonstration of high amyloid clearance. Among those drugs, two trials over four turned out to be positive on an 18-month primary clinical endpoint (EMERGE, TRAILBLAZER-ALZ, Table 1) and a third on 18-month secondary clinical endpoints (BAN2401-G000-201 whose primary clinical endpoint was prespecified after a 12-month duration). It contrasts with the previous clinical trials with anti-amyloid antibodies, which were consistently negative regarding their clinical outcome, except for the secondary outcomes of the EXPEDITION3 phase 3 solanezumab trial, and the exploratory analyses of the phase 2 bapineuzumab trial [43–46]. The main difference between this new generation of anti-amyloid clinical trials and the previous ones is their ability to induce a high clearance of amyloid load in the brains of patients selected on their clinical-biological profiles. The prior generation of anti-amyloid trials did not or barely induced clearance of Aβ pathology as measured with amyloid PET (the maximum being observed in a subgroup analysis of the amyloid PET positive individuals of the bapineuzumab 301 and 302 trials: −3.2% in the 1.0 mg/kg arm after 71 weeks while +3.4% was observed in the placebo arm; [47–49]). The previous generation of drugs and trials probably had a poor pharmacodynamic profile to achieve this goal (target of inappropriate Aβ species) or were used at too low doses for fear of ARIA. In contrast, the four new drugs and trials lowered the global amyloid load by 55–85 centiloids (see above) at the expense of ARIA. This high-clearance property seems to be the new empirical prerequisite of any anti-amyloid antibody before testing a clinical efficacy, and some authors now consider that amyloid load needs to be lowered to 20 centiloids or less to produce a noticeable cognitive benefit, with a lag time of several months between amyloid removal and clinical effect [50]. Thus, we decided to restrict our review and meta-analyses to these drugs because: 1) they were the only anti-amyloid antibodies to demonstrate a significant clinical effect, and; 2) these anti-amyloid antibodies are the only ones currently under development in sporadic symptomatic AD.

2.3. *Debate and meta-analysis regarding clinical efficacy*

The FDA officials defended and argued their decision to approve the aducanumab in position papers [51,52]. First, they acknowledged that ''the clinical trial data were not adequate on their own to convincingly demonstrate a clinical benefit in reducing the clinical decline in patients with Alzheimer disease'', closing the debate regarding the level of proof of the ENGAGE and EMERGE trials to demonstrate efficacy on cognitive decline. Second, they underlined that the recent positive results of the phase 2 trials on clinical outcomes

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Table 2 – Inclusion and exclusion criteria of completed or ongoing (gantenerumab) anti-amyloid therapies trials and US recommendations for an appropriate use of aducanumab in clinical practice. Adapted from [54].

Participant feature	Aducanumab		Lecanemab	Donanemab	Gantenerumab
	US recommendations for an appropriate use in clinical practice	Phase 3 clinical trials enrollment criteria	Phase 2 Clinical Trial Enrollment Criteria	Phase 2 Clinical Trial Enrollment Criteria	High-dose phase 3 clinical trials enrollment criteria (graduate 1 and 2 trials)
Age	Younger or older patients than studied in the ENGAGE and EMERGE trials (50–85 yo) meeting all other criteria for treatment could be considered candidates for aducanumab	50–85	50–90	60–85	50–90
Diagnosis	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or AD dementia
Scale scores at baseline	MMSE 21–30 or equivalent such as MoCA 17–30	CDR Global Score 0.5; MMSE 24–30; RBANS Delayed Memory Score of 85 or less	CDR Global Score 0.5–1; MMSE 22–30; Wechsler Memory Scale IV-Logical Memory (subscale) 2 < 1 SD	MMSE 20–28; CogState Brief Battery (learning/working memory score of 82 to 90)	CDR Global Score 0.5–1; MMSE 22–30; demonstrated abnormal memory function
Amyloid status	Amyloid positive PET (visual read) or CSF findings consistent with AD (low Aβ42, low Aβ42/Aβ40 ratio, abnormal Aβ42/tau ratios, or abnormal Aβ42/p-tau ratios)	Amyloid positive PET (visual read)	Positive biomarker for brain amyloid pathology (PET – visual read – or CSF tau/A-beta42)	Amyloid PET (florbetapir) SUVR > 1.17 (~37 centiloids)	CSF tau/A-beta42 or amyloid PET scan (visual read)
Tau status	Not assessed	Not assessed	Not assessed	Tau PET (flortaucipir) SUVR > 1.10 and < 1.46 (NB: for the phase 3 trial, high tau patients [SUVR > 1.46] are also included but will not be considered in the primary endpoint])	Not assessed
Genetic testing	APOE genotype determined	Consent for APOE genotyping	Consent for APOE genotyping	Consent for APOE genotyping	Consent for APOE genotyping
Neurological examination	Non-AD neurological disorders excluded	Non-AD neurological disorders, stroke, and TIA excluded	Excluded: any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD; TIA, stroke, or seizures within 12 months	Excluded: Modified Hachinski Ischemia Scale (MHIS) score of ≥ 4; any condition other than AD that may affect cognition; current serious or unstable neurologic disease (except AD)	Excluded: any condition other than AD that may affect cognition; history or presence of clinically evident cerebrovascular disease; history of severe, clinically significant CNS trauma; history or presence of an intracranial mass that could potentially impair cognition; presence of infections that affect brain function or history of infections that resulted in neurologic sequelae; history or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits

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Table 2 (*Continued*)

Participant feature	Aducanumab		Lecanemab	Donanemab	Gantenerumab
Cardiovascular history	Stable cardiovascular conditions required	Angina; myocardial infarction; congestive heart failure excluded; uncontrolled hypertension (systolic $>$ 165; diastolic $>$ 100)	Excluded: any unstable cardiovascular condition	Excluded: current serious or unstable cardiovascular disease; history of long QT syndrome (NB: history of long QT syndrome is no more an exclusion criterion in the phase 3 trial)	Excluded: clinically evident systemic vascular disease that in the opinion of the investigator has the potential to affect cognitive function; uncontrolled hypertension; unstable or clinically significant cardiovascular disease; myocardial infarction
Medical history	Stable medical conditions required; patients with history of autoimmune disorders or seizures excluded Normal serum vitamin B12 level, thyroid stimulating hormone (TSH), metabolic panel and liver function tests, complete blood count, comprehensive clotting studies and platelet count Normal erythrocyte sedimentaton rate and C-reactive protein	Excluded: clinically significant systemic illness; diabetes that cannot be managed; history of cancer unless in remission for 5 years or localized to skin or prostate; impaired liver function; hepatitis; HIV infection	Excluded: BMI $\leq$ 17 or $\geq$ 35; immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study; any other medical conditions which are not stably and adequately controlled, or which in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessments; HIV positive	Excluded: current treatment with immunoglobulin G therapy; current serious or unstable illnesses including retinal, hepatic, renal, gastroenterologic, respiratory, endocrinologic, immunologic, or hematologic disease; history of recent cancer except for cancers with low risk of recurrence or spread; vitiligo; positive HIV testing; multiple allergies; vision or auditive impairment interfering with cognitive testing; uncontrolled hepatitis B or C; impaired renal or liver function	Excluded: unstable or clinically significant kidney or liver disease; abnormal thyroid function; unstable diabetes; folic acid or B12 deficiency; unstable or clinically significant HIV infection, or hepatitis B; history of spirochete infection of the CNS; systemically, clinically significantly immunocompromised participants; current treatment with immunoglobulin therapy; history of recent cancer except for cancers with low risk of recurrence or spread; severe allergies; vision or auditive impairment interfering with cognitive testing
Psychiatric history	Stable psychiatrically	Unstable psychiatric illness in the past 6 months; alcohol or substance abuse in the past year; use of cannabinoids; positive urine tests for excluded substances	Any psychiatric diagnosis or symptoms that could interfere with study procedures in the participant; Geriatric Depression Scale (GDS) score $\geq$ 8 at screening; recent drug use disorder	Excluded: current serious or unstable psychiatric disease; history of schizophrenia or other chronic psychosis; any current primary psychiatric diagnosis other than AD likely to affect cognitive assessment, or affect the patient's ability to complete the study; serious risk for suicide; history of recent alcohol or drug use disorder	Excluded: history of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder; at risk for suicide
Reproductive status	Female subjects who are pregnant or breastfeeding excluded; female subjects who are of childbearing age must be practicing contraception	Female subjects who are pregnant or breastfeeding excluded; female subjects who are of childbearing age must be practicing contraception	Female subjects who are pregnant or breastfeeding excluded; female subjects who are of childbearing age must be practicing contraception or abstinence	Women of childbearing potential must be using or willing to use two forms of effective contraception	For women of childbearing potential: agreement to remain abstinent or use contraceptive methods

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Table 2 (*Continued*)

Participant feature	Aducanumab		Lecanemab	Donanemab	Gantenerumab
Clotting status	Patients with bleeding disorders or on anticoagulants excluded	Bleeding disorders, anticoagulants, and antiplatelets (besides low-dose Aspirin) excluded	Bleeding disorders and anticoagulants allowed if stable	No restriction regarding bleeding disorders and anticoagulants	Bleeding disorders, anticoagulants excluded
Concomitant medications	Patients can be on standard of care with cholinesterase inhibitors and memantine	Cholinesterase inhibitors and memantine allowed	Stable cholinesterase inhibitors and memantine allowed; Stable concomitant medications that could potentially affect cognition	Stable cholinesterase inhibitors and memantine allowed; Stable concomitant medications that could potentially affect cognition; CYP3A inhibitors; drugs known to significantly prolong the QT interval	Stable cholinesterase inhibitors and memantine allowed; Stable concomitant medications that could potentially affect cognition
Contraindication to MRI	Excluded	Excluded	Excluded	Excluded	Excluded
Baseline MRI	None of the following: acute or subacute hemorrhage; macrohemorrhage; cortical infarction larger than 1.5 cm; one lacunar infarction larger than 1.5 cm; more than four microhemorrhages; more than one area of superficial siderosis; extensive white matter disease indicative of ischemic injury	Baseline MRI finding that excluded participation: acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (> 1.5 cm), 1 lacunar infarction (> 1.5 cm), superficial siderosis, or diffuse white matter disease	Clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD; baseline MRI including but not limited to: more than 4 microhemorrhages; a single macrohemorrhage > 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space-occupying lesions; or brain tumors	Baseline MRI finding that excluded participation: evidence of significant abnormality that would suggest another potential etiology for progressive dementia; presence of ARIA-E, greater than 4 cerebral microhemorrhages, more than one area of superficial siderosis or severe white matter disease	Baseline MRI finding that excluded participation: $\geq$ 2 lacunar infarcts, any territorial infarct > 1 cm^3, diffuse white matter disease, > 5 combined microbleeds and areas of leptomeningeal hemosiderosis
Care support	May be living independently or with a care partner	Reliable informant or care partner	Have an identified study partner	Have a study partner who is in frequent contact with the patient, and will accompany the patient to study visits or be available by telephone at designated times	Availability of a reliable study partner who accepts to participate in study procedures throughout the 2 years duration of study

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Table 2 (*Continued*)

Participant feature	Aducanumab		Lecanemab	Donanemab	Gantenerumab
Informed consent	Patient and care partner must understand the nature and requirements of therapy (e.g., monthly infusions to be performed indefinitely) and the expected outcome of treatment (removal of amyloid and slowing of decline of clinical features)	Must be signed by participant and care partner	Must be signed by the participant and/or care partner	Have a study partner who will provide written informed consent to participate	Must be signed by participant and care partner
Drug administration	IV, once every 4 weeks (titration)	IV, once every 4 weeks (titration)	IV, once every 2 weeks	IV, once every 4 weeks (titration) – lowered and discontinued once a negative amyloid PET is reached	SC, once every 4 weeks (titration). NB: a parallel phase 2 trial of gantenerumab is currently testing the pharmacokinetics effects with a weekly infusion of 255 mg.gantenerumab
MRI monitoring	Systematic: prior to 5th, 7th, 9th and 12th doses Optional: if any symptoms suggestive of ARIA occur	Systematic: prior to 5th, 7th, 9th, 12th, 15th doses and two weeks after the last infusion Optional: unscheduled visit for ARIA	Systematic: prior to 5th, 7th, 14th, 20th, 27th, 33rd, 40th doses and two weeks after the last infusion Optional: unscheduled visit for ARIA	Systematic: just after the 2nd dose, before the 4th dose, just after the 5th, 7th, 10th, 14th doses and four weeks after the last infusion Optional: unscheduled visit for ARIA	Systematic: prior to 4th, 7th, 10th, 13th doses Optional: unscheduled visit for ARIA

AÔ: amyloid-beta protein; AD: Alzheimer's disease; APOE: apolipoprotein E; BMI: Body Mass Index; CDR: Clinical Dementia Rating; cm: centimeter; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; IV: intravenous; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; PET: positron emission tomography; PRES: posterior reversible encephalopathy syndrome; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; SC: subcutaneous; SD: standard deviation; TIA: transient ischemic attack.

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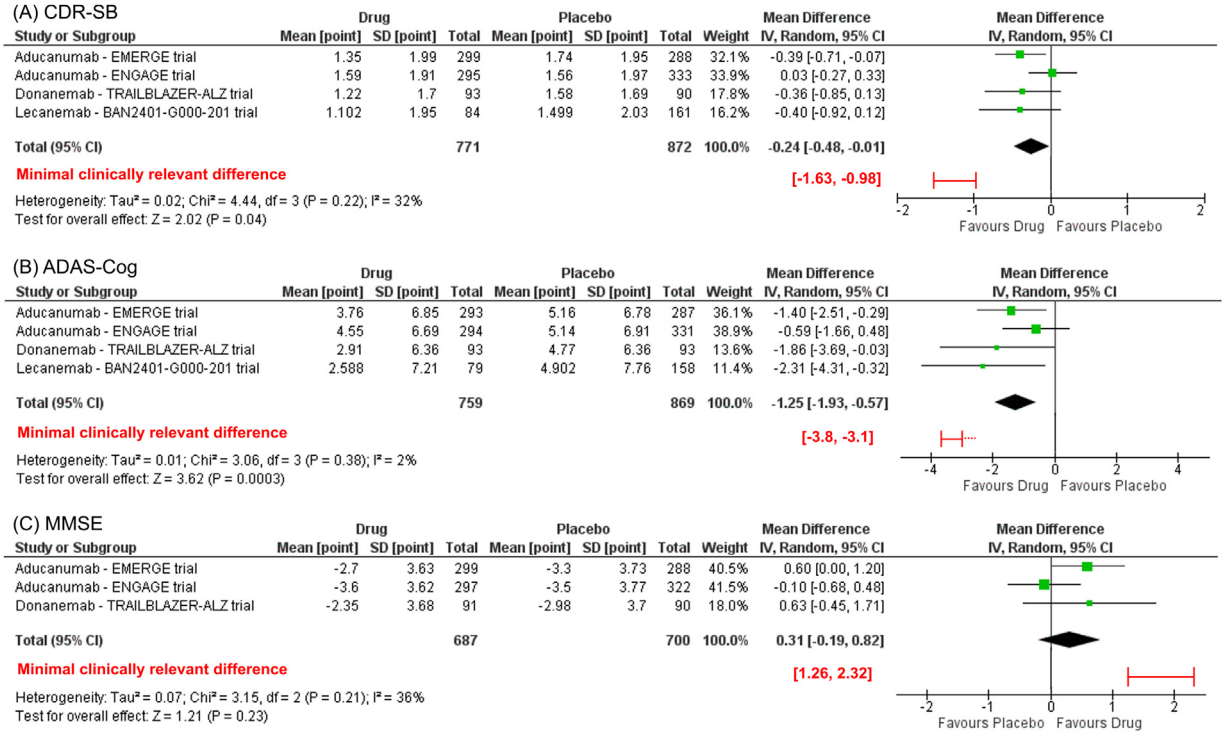

Fig. 1 – Meta-analysis of the effect of high-clearance anti-amyloid antibodies on main clinical outcomes at 18 months in the highest dose groups (high dose adaptative arm for aducanumab, 10 mg/kg bi-weekly for lecanemab, and donanemab unique adaptative dose). Forrest plot of comparisons between drugs and placebo on several cognitive tests: CDR-SB (A), ADAS-Cog (B), and MMSE (C). The sample sizes reflect the patients with a completed 18-month follow-up. Analyses were performed using the Cochrane-recommended publicly available software (RevMan 5.4.1) with a Random Effect Model. The minimal clinically relevant values are taken from the literature (see text for details) [55,56]. For the ADAS-Cog, the dotted line outside the 3.1–3.8 range represents the putative minimal clinically relevant values in the high-clearance anti-amyloid immunotherapies trials' populations, i.e., earlier AD stages than in the Schrag & Schott publication [56].

from donanemab and lecanemab were supportive findings of the ENGAGE and EMERGE trials.

To test this assertion, we performed a meta-analysis of the high-dose groups from lecanemab and donanemab phase 2 trials and the aducanumab phase 3 trials. We performed this meta-analysis on the effect of the drug on the shared cognitive tests used in these three trials (CDR-SB and ADAS-Cog; MMSE was only performed with the donanemab and aducanumab trials' results), on the planned 18-month endpoint, and only on the highest dose group (i.e., the groups used for approval application or ongoing phase 3 trial: see above for details). Analysis was performed using the Cochrane-recommended publicly available software (RevMan 5.4.1), using a Random Effect Model due to the heterogeneity of the collected data (phase 2 and 3 trials; some discrepancies between inclusion and exclusion criteria – see Table 2). Results are detailed in Fig. 1. Briefly, this meta-analysis supported the FDA officials' assertion and proved a significant global effect of high-clearance anti-amyloid immunotherapies on the progression of CDR-SB, ADAS-Cog, but not of MMSE (Fig. 1). The results were also significant on the same scales when using Fixed-Effect models (see Online material Supplementary Fig. S1). We confirmed these findings using a generic inverse variance approach, i.e., entering directly the difference estimates and their error intervals as calculated in the original articles using multivariate models. This only marginally changed the results (Online material Supplementary Fig. S2). Finally, we performed a Bayesian meta-analysis (using the freely available software JASP v0.16.1), which gave very similar results (Online material Supplementary Fig. S3). The Bayes factors (BF) underlined that the results showing a benefit of high clearance anti-amyloid immunotherapies were the most convincing on the ADAS-Cog ($BF_{10} = 36.1$) while being significant (but anecdotal) for the CDR-SB ($BF_{10} = 1.2$) and slightly in favor of the null hypothesis for the MMSE ($BF_{10} = 0.6$) (Online material Supplementary Fig. S3). Such a meta-analysis should not substitute the agency gold standards for drug approval, i.e., two positive phase 3 randomized-control trials, and should not add any confusion to this debate. Nonetheless, it confirms the trend regarding the clinical efficacy of high-clearance anti-amyloid immunotherapies and offers the opportunity to estimate the magnitude of the clinical effect of high-clearance anti-amyloid immunotherapies [15,53].

The weighted-mean 18-month slowing of cognitive decline under high-clearance anti-amyloid immunotherapies on CDR-SB reaches −0.24 points (95% confidence interval [CI] −0.48–

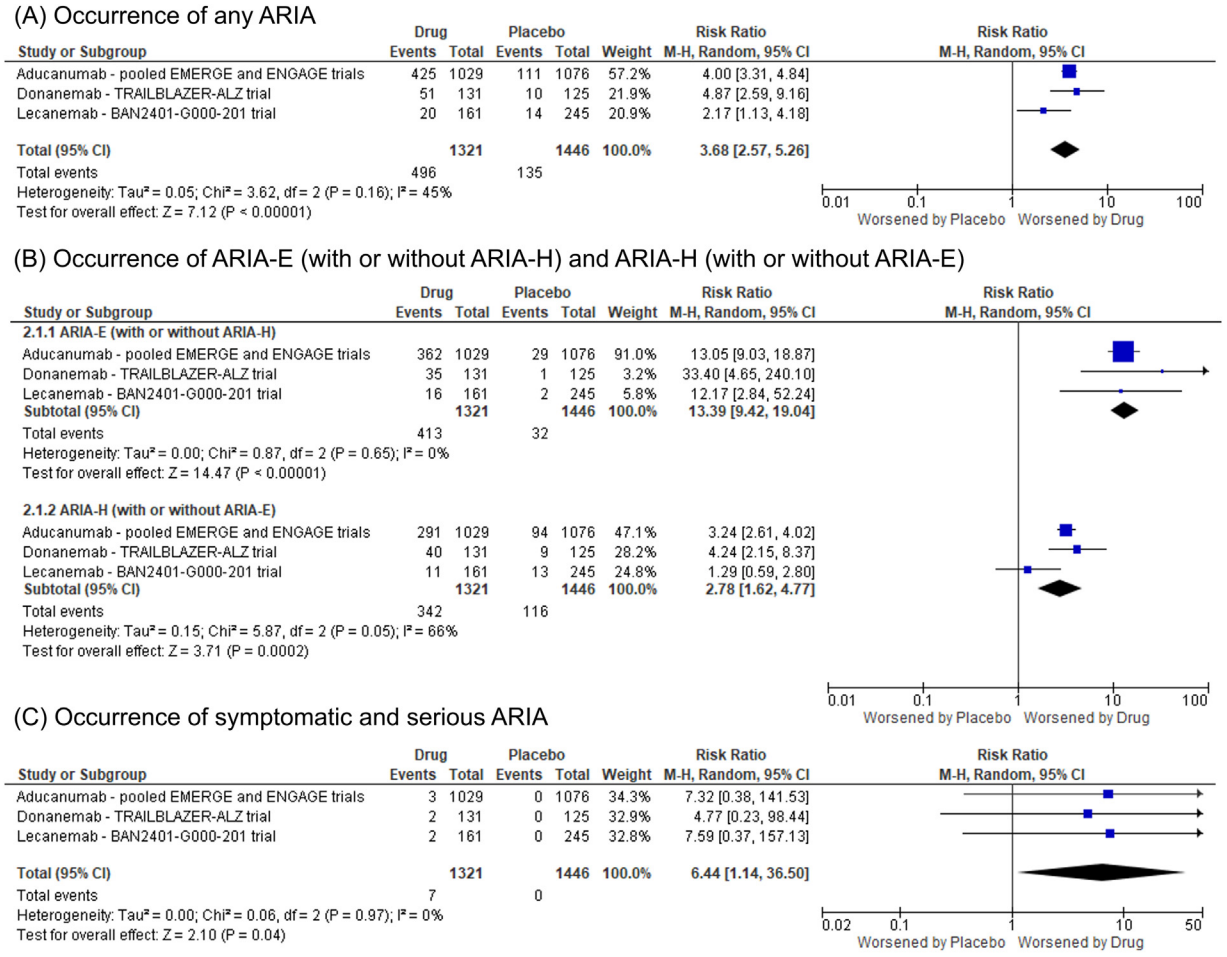

Fig. 2 – Meta-analysis of the occurrence of the main side effects (amyloid-related imaging abnormalities [ARIA] edema [E] and/or hemorrhage [H]) under high-clearance anti-amyloid antibodies in the highest dose groups at 18 months (high dose adaptative arm for aducanumab, 10 mg/kg bi-weekly for lecanemab, and donanemab unique adaptative dose). Forrest plot of comparisons between drugs and placebo on ARIA-E and ARIA-H expressed as risk ratios. A. Occurrence of any ARIA (ARIA-E or ARIA-H). B. Subgroup analysis: occurrence of ARIA-E (with or without ARIA-H) and ARIA-H (with or without ARIA-E). C. Occurrence of symptomatic and serious ARIA. The sample sizes reflect the patients with a completed 18-month follow-up. Analyses were performed using the Cochrane-recommended publicly available software (RevMan 5.4.1), with a Random Effect Model and Cochran-Mantel-Haenszel statistics.

−0.01 points), −1.25 points (95% CI −1.93–−0.57 points) on the ADAS-Cog, and +0.31 points (95% CI −0.19–0.82 points) on the MMSE (not significant – data not available for the lecanemab trial) in the highest dose groups (Figure 1). These values are below the minimal clinically relevant difference for clinical outcomes that have been estimated for AD patients in 2019 on a one-year follow-up using anchor-based (change in outcome linked to clinical opinion) and distribution-based (minimal clinically relevant difference calibration based on the variation across participants) approaches, stratified by severity of cognitive impairment [55]. The minimal clinically relevant differences increased with disease severity. For MCI and mild AD, differences of 0.98 and 1.63 points for CDR-SB and 1.26 and 2.32 points for MMSE represented clinically meaningful change. Regarding ADAS-Cog, a 2012 study estimated that the minimally clinically relevant change could be around 3 points in mild AD patients (3.1–3.8), again above what has so far been observed with high-clearance anti-amyloid immunotherapies [56]. The cognitive effect of high-clearance anti-amyloid immunotherapies after 18 months is also smaller than the effect of 10 mg donepezil after six months in mild-to-moderate clinically defined AD (−0.53 points on CDR-SB; +1.05 points on MMSE) [57]. Besides, in individuals corresponding to the inclusion criteria of the EMERGE and ENGAGE trials, the natural heterogeneity in disease progression is broad in the absence of any treatment: −0.35 to +0.35 points (95% range) of variability in CDR-SB evolution over 18 months [58]. Most of the effect sizes in the cited positive trials fall within this 95% range, suggesting that the trials' design for these drugs may not be optimal in its current form for patients with early symptomatic AD, using the CDR-SB as the primary endpoint and an 18-month follow-up.

On the other hand, we have to keep in mind that the mean yearly cognitive evolution of the placebo group in these trials

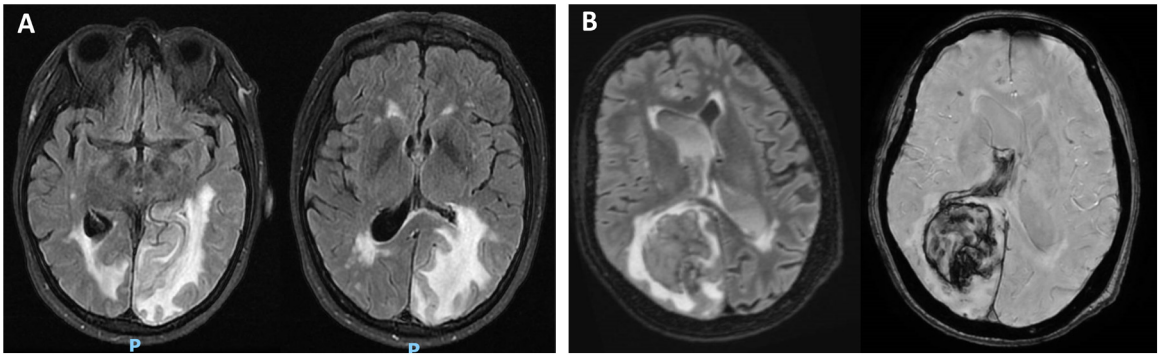

Fig. 3 – Illustration of serious symptomatic ARIA under lecanemab (Clarity AD ongoing phase 3 trial). A. FLAIR brain MRI of a 69-year-old woman, biologically-proven amnesic AD, APOE ε4 carrier, massive ARIA-E responsible for a partial status epilepticus occurring after four months of treatment. The status epilepticus was then complicated by a post-ictal Tako-Tsubo responsible for acute heart failure, confusion responsible for a fall, an unstable T12 vertebral fracture, and an L5 vertebral fracture. MMSE one month before ARIA: 25/30, MMSE eleven months after ARIA: 16/30. B. FLAIR and SWI brain MRIs of a 70-year-old woman, biologically-proven amnesic AD, APOE ε4 carrier, massive ARIA-H (7 cm hematoma) revealed by an acute headache occurring after two months of treatment and at one month of suspension of infusions for ARIA-E discovered incidentally on follow-up MRI. The patient was on an effective dose of apixaban. MMSE three months before the first infusion: 25/30, MMSE seven months after ARIA: 13/30, sequela hemianopia (Dr. Nicolas Villain, personal communication).

(CDR-SB = +1.0 – +1.16 points/year, ADAS-Cog +3.18 – +3.44 points/year, MMSE = −2.0–−2.3 points/year: see Table 1) is close to the minimal clinically relevant differences highlighted above. Thus, after an 18-month follow-up, a minimally clinically relevant effect would only be observed if the drug is responsible for an almost complete stop of the progression of the disease.

A more significant effect might be expected after a longer follow-up, given these drugs' expected ''disease-modifying'' property, as suggested by the long-term small sample data from the PRIME study extension and the lecanemab open-label extension [35,59]. However, the level of evidence of these data remains currently very weak. Under such assumption and a constant effect of the treatment over time, one might thus expect that a minimally relevant clinical effect of high-clearance anti-amyloid immunotherapies could be observed after 6–10 years under treatment. Another essential point to underline is that the clinical effects measured in the ENGAGE and EMERGE trials may be limited by the small number of individuals under the highest 10 mg/kg dose regimen. Indeed, the late amendment for APOE ε4 carriers, the early termination of the studies, the high rate of ARIA occurrence (implying a slower titration, a dose lowering, or a treatment suspension), and the long titration protocol have all contributed to lower the total duration under a 10 mg/kg dose [12,60–65].

2.4. *Safety and ARIAs in high-clearance anti-amyloid immunotherapies trials*

As emphasized by the EMA, the major safety concern for anti-amyloid antibodies is ARIA. This concern was identified with the first low-clearance anti-amyloid immunotherapies and carefully monitored in subsequent trials [4]. However, in high-clearance anti-amyloid immunotherapies trials, the ARIA rate was much higher than observed within low-clearance anti-amyloid antibodies trials: 41.3% of ARIA occurrence in the 10 mg/kg group from the pooled ENGAGE and EMERGE trials (vs. 10.3% in the placebo group; [12]), 38.9% in the donanemab trial (vs. 8.0% in the placebo group), and 12.4% in the high-dose group from the lecanemab trial (vs. 5.7% in the placebo group). In the pooled data from the bapineuzumab studies, ARIA-E rate reached up to 15.3% (vs. 0.2% in the placebo group; [66]), 13.5% in the pooled low-dose gantenerumab trials (vs. 0.8% in the placebo group; [48]), and 0.1% in the solanezumab trials (vs. 0.2% in the placebo group; [49]).

We also performed a meta-analysis of the ARIA occurrence in the high dose groups of high-clearance anti-amyloid immunotherapies trials. The rate of occurrence of any ARIA, ARIA-E, or ARIA-H was significantly increased by high-clearance anti-amyloid immunotherapies (Fig. 2). In detail, the magnitude of the effect was the highest for ARIA-E (RR = 13.4; 95%CI 9.42–19.04; $P < 0.001$). The Fixed-Effect models and the Bayesian approach gave comparable results (Online material Supplementary Figs. S4 and S5). Again, since the vast majority of data regarding ARIA come from the pooled data from the aducanumab trials, one has to keep in mind that these trials were designed to decrease the occurrence and severity of ARIA (see above) and used a close radiological and clinical monitoring and management of ARIAs. In the aducanumab trials, ARIA led to treatment discontinuation in 6.2% of patients (0.6% of patients on placebo). Most ARIA events (74%) detected by MRI were asymptomatic. Among those with symptomatic ARIA, symptoms were mild in 67.7%, moderate in 28.3%, severe in 4%, and serious in 0.3%. The most common symptoms reported were confusion or altered mental status (5%), dizziness (4%), visual disturbances (2%), and nausea (2%) [12]. ARIA episodes typically resolved in 4–16 weeks [67]. Since ARIA is often considered a minor issue as it can be fully reversible if handled by close monitoring and dose adjustment [64,68], we also reported the meta-analysis of the symptomatic and

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serious ARIA events in high-clearance anti-amyloid immunotherapies trials (Fig. 2C). Seven events (0.5%) were identified across the four trials (vs. 0.0% in the placebo groups), which confirms a rare but significant and important effect of high-clearance anti-amyloid immunotherapies (RR = 6.4; 95%CI = 1.14–36.0; $P = 0.04$). Using a fixed-effect model did not change the results (Online material Supplementary Fig. S4). The Bayesian approach halved the RR estimate with a 95% confidence interval encompassing 1 (RR = 3.0; Bayesian 95%CI 0.7–18.2), but with a Bayes factor still in favor of an effect of the drug beyond the null hypothesis ($BF_{10} = 1.8$) (Online material Supplementary Fig. S5). Two personal and so far unpublished cases from the ongoing lecanemab Clarity AD phase 3 trial illustrate that this phenomenon, though rare, should not be undermined and can be responsible for long-term sequelae (Fig. 3). Besides, this occurred despite the strict exclusion criteria and close monitoring of clinical trials. In real-life clinical practice, this risk might be increased.

Currently identified risk factors for ARIA in the aducanumab trials are the APOE status (with $\varepsilon 4$ carriers being more prone to ARIA, and following an allele-dose effect; HR 2.5: 95% CI, 1.90–3.20) and the baseline microbleed count (HR 1.7; 95%CI, 1.31–2.27) [12,68,69]. These trials were performed with strict exclusion criteria regarding comorbid cerebrovascular conditions, vascular risk factors, and concomitant antithrombotic medications (Table 2). Other ARIA risk factors identified from the low-clearance immunotherapies trials were: the effect of antibody (with the notable example of solanezumab that does not induce an increased risk of ARIA) and a dose-effect [9,10,68,69].

3. The debate regarding the FDA aducanumab accelerated approval

3.1. Indications and contra-indications

Supportive physicians of the FDA decision underlined that the FDA notice regarding indications and contra-indications of aducanumab was too broad [64]. Indeed, on June 7th 2021, the initial FDA notice of aducanumab only mentioned in the indication of the drug: ''Alzheimer's disease'', without reference to the stage nor to the demonstration of a positive amyloid biomarker and without mentioning the contra-indications (especially the ARIA risk factors that were considered as exclusion criteria in the EMERGE and ENGAGE trials). This notice was updated at the beginning of July and now mentions ''MCI due to AD'' and ''mild AD dementia'' instead of ''Alzheimer's disease'' but still does not mention the use of a positive amyloid biomarker or the exclusion criteria of the ENGAGE and EMERGE clinical trials. Finally, an American expert panel proposed to narrow the indications of aducanumab to the inclusion and exclusion criteria of the ENGAGE/EMERGE trials, adapted to clinical practice (e.g., the use of CSF low Aβ is permitted instead of amyloid PET to determine the amyloid status) [54,64] (see Table 2 for details).

3.2. Surrogacy: the concept behind the approval of aducanumab

The FDA officials defended that the current ''Accelerated Approval'' status was in line with its use for aducanumab approval since ''Accelerated approval'' is permitted when four requirements are met: 1) the drug must be for treatment of a serious disease with unmet medical needs; 2) the drug must be expected to provide a meaningful clinical advantage over available therapy; 3) there must be an effect of the drug on a surrogate endpoint (typically, that reflects the underlying pathology of the disease); 4) there must be a determination that it is reasonably likely that the effect on the surrogate endpoint predicts clinical benefit of the drug. ''Reasonably likely to predict'' a clinical benefit is the specific wording of the status, not ''certain to provide benefit'' [52]. In aducanumab's particular case, surrogate markers are represented by the changes (decrease) in the amyloid load, reflecting the expected impact of the treatment on a critical node of the AD pathophysiological biological cascade (the ''amyloid cascade''), leading to slow, stop or reverse the cognitive decline.

Therefore, one crucial issue is to ensure that the ''amyloid cascade'' hypothesis sufficiently supports amyloid load as a surrogate marker. A large amount of scientific data supports the harmful role of Aβ 42 oligomers and plaques in AD and gives biological plausibility to the aducanumab efficacy. This literature emerged in the 1990s after identifying the genes involved in the autosomal dominant forms of AD, which were all located on the amyloid pathway [70–77]. It then led to the amyloid cascade hypothesis, which postulates that Aβ is the trigger of the pathogenic cascade that then leads to tau pathology, neurodegeneration, and symptoms [78]. This theory received numerous pieces of evidence from fundamental neuroscience or clinical studies [79]. Ultimately, this hypothesis led to the proposal by the NIA-AA in 2018 to define AD based only on the positivity of biomarkers (tau and amyloid) and focusing on the role of Aβ in defining the Alzheimer continuum [80]. However, there is also an almost as large amount of literature that criticizes this hypothesis and proposes alternative probabilistic models and definitions for AD based on the observation of: 1) earlier tau than Aβ pathology in neuropathological series; 2) weak relationships between Aβ and clinical symptoms; 3) a low predictive value of Aβ biomarker positivity on cognitive decline in non-autosomal dominant forms of AD [81–84]. Ultimately, the only validation of the therapeutic part of the amyloid cascade hypothesis is that benefits are demonstrable in clinical trials.

Another issue regarding surrogacy is its importance in agencies' validation process of a drug or medical device. Indeed, beyond the agency's definition and appraisal of surrogacy, several methodologists have discussed these aspects and proposed scales or criteria that aim to validate the use of surrogate markers as endpoints in clinical trials [85–88]. Applied to the use of amyloid load, measured with PET, as a surrogate endpoint in clinical trials in patients with AD, the FDA appraisal of surrogacy has generated a lot of controversies [89,90]. While there is no debate regarding the effect of aducanumab on amyloid load, the relationship between amyloid load and cognitive decline in AD remains highly debated [82]. Besides, even if Aβ is an excellent biomarker of

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AD and predicts progression, it does not necessarily say anything definitive about Aβ removal and clinical benefit. In the ENGAGE and EMERGE trials, only a weak significant correlation was observed in the EMERGE study when pooling low- and high-dose groups (partial Spearman correlations: $|\rho| = 0.19–0.29$), but not in the ENGAGE study ($|\rho| = 0.02–0.09$) [11]. These correlations were not significant within the high-dose groups even when pooling the ENGAGE and EMERGE trials [91]. This lack of correlation was also observed in the donanemab trial [92]. Finally, it is interesting to note that in 2018 both the FDA and the EMA underlined that ''Currently, there is no consensus as to particular biomarkers that would be appropriate to support clinical findings in trials in early AD'' in guidelines for the industry regarding the development of drugs for the treatment of AD [93,94]. However, three years later, another conclusion emerged from the FDA without any new evidence in the literature.

Some authors also point out that this ''Accelerated Approval'' pathway should be reformed [95,96]. It should specify the use of validated surrogate markers according to a strict methodology, the validation study should be established and initiated before the start of drug use, an improved rigor in the follow-up of confirmatory studies should be implemented, and the conditions of drug use should be more similar to study inclusion and exclusion criteria. This argument might also apply to the EMA expedited approval pathways (including conditional marketing authorization [CMA] and accelerated assessment [AA]) since marketing authorizations for products granted CMA or AA between 2011 and 2018 were based dominantly on unvalidated surrogate endpoints [97].

3.3. *The medical-economical aspect*

The initial price set up by Biogen® for the US market regarding aducanumab was USD 56,000/year for a 70 kg patient. Therefore, it is reasonable to also discuss the benefit of this drug from a medical-economic standpoint. This dimension is quite challenging to evaluate, although some tools may be helpful. The quality-adjusted life-year (QALY) is a generic measure of disease burden, including the quality and the quantity of life lived for a given individual [98]. It is used in economic evaluations to assess the value of medical interventions. One QALY equates to one year in perfect health. The US Institute for Clinical and Economic Review (ICER) has determined that in the US, the maximum value a single QALY can have in dollars is USD 150,000 [99]. It made that calculation based on various health-economics studies on how much Americans are willing to pay for their health care and how health care spending compares per capita worldwide.

Herring and colleagues (three co-authors of this paper being Biogen®'s employees [100]) estimated that, when only considering the clinical efficiency of the EMERGE study, over a lifetime horizon, aducanumab treatment corresponded to 0.65 incremental patient QALYs and 0.09 fewer caregiver QALYs lost compared with patients treated with standard of care. Whittington and colleagues estimated that, based on the pooling of data from both EMERGE and ENGAGE trials, over the lifetime time horizon, treating a patient with aducanumab results in 0.15 more QALYs gained per patient [101]. Similar findings were found by Ross and colleagues for aducanumab (0.13 lifetime QALY gained), while they estimated this gain to be slightly higher for donanemab (0.41 lifetime QALY gained) [102]. Moreover, ICER performed the cost assessment regarding the effectiveness and value of aducanumab in May 2021, before the approval by the FDA and the annual USD 56,000 price being set up by Biogen®. ICER concluded that an annual cost of $50,000 for aducanumab would not properly align with its clinical benefits, even under the optimistic assumption of effectiveness only driven by the EMERGE study. In this case scenario, USD 56,000 for aducanumab would represent about 368,000–389,000 USD/QALY, much more than what the ICER considers the maximum value of a single QALY [103]. ICER confirmed its judgment that evidence is insufficient to demonstrate the net health benefit of aducanumab for patients with Alzheimer's disease in a revised evidence report (after aducanumab approval and taking into account the actual price and number of MRIs for follow-up: [104]). Whittington and colleagues estimated that at the list price of $56,000 per year, the cost-effectiveness was $1.33 million per QALY gained from the health care system perspective and $1.27 million per QALY gained from the modified societal perspective [101]. On December 20th 2021, Biogen® decided to halve the price for the US market to USD 28,000/year [105]. Using the same approach as Whittington and colleagues, but with the updated $28,000 price, Ross and colleagues estimated the cost-effectiveness to be $981,000 per QALY gained from the health care system perspective, and $964,000 per QALY gained in the modified societal perspective [102]. The same authors estimated these figures to be $193,000/QALY and $176,000/QALY, respectively, for donanemab under the assumption of an annual $28,000 price and of a switch to placebo after substantial amyloid reduction on PET imaging (27% of patients at six months and 55% of patients at twelve months) [102]. In comparison, treating AD dementia with a rivastigmine transdermal patch has a cost-effectiveness ratio of $93,000 per QALY compared to donepezil monotherapy in the US healthcare system [106].

However, the cost per QALY should not be seen as a gold standard for drug cost-effectiveness reviews [107]. Indeed, this value is highly variable from one healthcare system to another: first, regarding the cost of a given drug, and second, for example, the willingness-to-pay thresholds per QALY are variable. The willingness-to-pay thresholds per QALY are considered to be around 20,000–50,000 pounds for the UK (US$25,000–65,000), 20,000–100,000 CAD for Canada (US $16,000–80,000), and 40,000–75,000 AUD for Australia (US $32,000–60 000) [108].

Regarding payers, in April 2022, the CMS disclosed a final decision memo for the coverage of FDA-approved anti-amyloid immunotherapies [109]. Briefly, it states that Medicare will differentially cover high-clearance anti-amyloid immunotherapies for the treatment of AD according to their level of proof. FDA-approved drugs based on a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies (whose data may simply be collected in a registry), while FDA-approved drugs based on a surrogate endpoint may be covered in an NIH-, FDA-, or CMS-approved randomized controlled trial. Besides, contrary to the FDA notice, it proposes that this coverage applies only to patients with MCI due to AD or mild AD dementia with confirmed presence of Aβ pathology. In line with numerous US scientists

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and physicians, the CMS also underlined that the ENGAGE and EMERGE trials lacked racial/ethnic diversity [110,111]. Therefore, there is little evidence that aducanumab is safe or effective for people of all racial/ethnic groups, a major problem in multi-ethnic countries such as the US. This decision memo has discouraged Roche®, but not Eisai® and Eli Lilly®, regarding an Accelerated Approval application (see above) [31,36,42]. This decision will strongly impact the commercialization of aducanumab in the US in the short term since only patients included in NIH-, FDA-, or CMS-approved trials will be covered by Medicare. Biogen® or any other drug company might now sue Medicare over the decision by arguing that Medicare does not have the legal authority to require more studies to prove companies' drugs benefit patients [112]. Regarding private health insurance, half-a-dozen private health insurers in some of the largest US states are balking at covering aducanumab [113,114]. Geriatricians have also claimed that investing the same amount of money not to reimburse aducanumab but into programs that have already proven to help people living with dementia would be more efficient [115]. Finally, the US Alzheimer's Association applauded the FDA decision though criticized the drug's high price and the CMS decision to limit coverage [116,117].

Nine months after approval, the prescription of aducanumab in the US was much more limited than expected [118]. Beyond the US, the United Arab Emirates and Qatar recently approved the therapy [119,120], and the Japanese drug agency is currently examining the aducanumab's application and is asking for more data before conclusion [121].

4. Conclusion

Aducanumab's approval by the FDA has generated an unprecedented debate in the field, and contradictory agencies' decisions. Beyond controversies and non-trivial medico-economical considerations, the pooled data from high-dose aducanumab, lecanemab, and donanemab trials (three drugs that have proved to induce a high clearance of brain amyloid load) tend to confirm that a statistically significant but slight clinical effect of these drugs emerges in patients with early AD after 18 months. Besides, safety data analysis confirms that these drugs are responsible for an important risk of ARIA, which can seldom, but beyond chance, be serious with long-term sequelae. The risk/benefit ratio of this class of drugs in early AD remains so far questionable after 18 months. Identifying subgroups of better responders, the perspective of combination therapies, and a longer follow-up may help improve their clinical relevance, but data are currently lacking. Three of these drugs are now under examination or approved under an ''Accelerated Approval'' pathway in the US, and five high-clearance anti-amyloid antibodies have ongoing (or planned) phase 3 trials in early AD.

In ''part 2'' of this review, we will discuss the possible schedule for a putative approval of these drugs in France, their possible indications and contra-indications, and their implementation in the French healthcare system (reference to part 2).

Disclosure of interest

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During the past three years, VP was a local unpaid investigator or sub-investigator for the following trials: Evoke and Evoke+ (NCT04777396, NCT04777409, NovoNordisk), Tango and Embark (NCT03352527, NCT04241068, Biogen), Lucidity (NCT03446001, TauRx Pharmaceuticals), Autonomy (NCT04619420, Janssen), Green Memory (NCT04520412, Green Valley Pharmaceuticals). He received Research grants from Fondation Bettencourt Schueller (CCA-Inserm-Bettencourt).

RL is an unpaid principal investigator or sub-investigator in numerous clinical trials involving Biogen®, Roche®, Eisai®, Eli Lilly®, Janssen–Johnson & Johnson®, Alector®, MagQu®... Besides he receives research grants from public and private fundings, not including pharmaceutical companies or foundations supported by pharmaceutical companies.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.plantsci.2004.08.011.

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