High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France

Nicolas Villain, V Planche, R Levy

Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com

General review

High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France

N. Villain [a,b,*], V. Planche [c,d], R. Levy [a,b]

[a] AP–HP Sorbonne Université, Hôpital Pitié-Salpêtrière, Department of Neurology, Institute of Memory and Alzheimer's Disease, Paris, France
[b] Sorbonne Université, INSERM U1127, CNRS 7225, Institut du Cerveau - ICM, Paris, France
[c] University Bordeaux, CNRS, IMN, UMR 5293, 33000 Bordeaux, France
[d] Centre Mémoire Ressources Recherches, Pôle de Neurosciences Cliniques, CHU de Bordeaux, 33000 Bordeaux, France

INFO ARTICLE

Article history:
Received 18 February 2022
Received in revised form
20 July 2022
Accepted 13 August 2022
Available online xxx

Keywords:
Alzheimer
Immunotherapy
Amyloid
Aducanumab
Donanemab
Lecanemab
Gantenerumab

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 II trials, and five drugs are being studied in phase III trials. Lecanemab is currently under examination for an 'Accelerated Approval' in the US, with an expected decision in January 2023. The common feature and novelty of these anti-amyloid immunotherapies, compared to those tested in previous trials of the 2010s, 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. In the first part of this review, we underlined through a meta-analysis that the pooled data from high-clearance anti-amyloid immunotherapies trials demonstrated a significant but slight clinical effect after 18 months. Still, safety remains an issue with serious and symptomatic amyloid-related imaging abnormalities, which are seldom (~1 per 200 treated patients) but occur beyond chance. In the second part of this review, we hypothesized that there is a high probability that some phase III trials of high-clearance anti-amyloid immunotherapies in early AD will finally be unarguably positive on clinical outcomes in the next five years with acceptable safety data. This may, in turn, lead to approval by the European Medicine Agency if the risk-benefit profile is deemed favorable. Such approval

* *Corresponding author*. Institut de la Mémoire et de la Maladie d'Alzheimer, Département de Neurologie, Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75651 Paris cedex 13, France.
E-mail address: nicolas.villain@aphp.fr (N. Villain).

https://doi.org/10.1016/j.neurol.2022.08.002

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

would be a game-changer in managing AD patients and for the organization of memory clinics in France. We review the possible timeline and scenarios for putative approval in France and make propositions regarding putative use in clinical practice, putative implementation in a real-life setting, and ethical considerations.

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 standard approval, and Biogen® withdrew its appeal against the EMA decision in April 2022. The Centers for Medicare & Medicaid Services (CMS) decided to severely limit the drug coverage in the US in April 2022 [1]. Despite the controversy around aducanumab's approval, the recent positive results of the phase II trials regarding other high-clearance anti-amyloid immunotherapies, lecanemab, and donanemab, suggest that European approval of one of these drugs is probable in the forthcoming five years. If it happens, such approval will be a game-changer in managing AD patients and for the organization of memory clinics in France: from diagnosis and use of biomarkers to monitoring and follow-up of these treatments.

This two-part 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 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. In the first part, we thoroughly reviewed the current evidence regarding high-clearance anti-amyloid immunotherapy. We saw that aducanumab's approval by the FDA has generated an unprecedented debate in the field. Beyond controversies and non-trivial medico-economic considerations, the pooled data from high-dose aducanumab, lecanemab, and donanemab trials confirmed a significant but slight clinical effect of these drugs in patients with early AD after 18 months [1]. Besides, safety data analysis confirmed that these drugs are responsible for an important risk of amyloid-related imaging abnormalities (ARIA), which can seldom (~1 per 200 treated patients), but beyond chance, be serious and symptomatic with long-term sequelae. Two of these three drugs have been approved or are currently under examination for 'Accelerated Approval' in the US, and five high-clearance anti-amyloid immunotherapies have ongoing (or planned) phase III trials in early AD. This second part will now discuss the possible timeline and scenarios for approval in France, recommendations for putative use in clinical practice, practical implementation issues, and ethical considerations.

1. Possible timeline and scenarios before putative use of high-clearance anti-amyloid immunotherapies in clinical practice in France

As detailed in the first part of this review [1], in December 2021, the EMA went against the FDA decision and recommended refusal of marketing authorization for aducanumab [2]. Biogen® appealed this decision, and the Committee for Medicinal Products for Human Use (CHMP) re-examined the application and 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 on April 22nd, 2022. Only the EMA can decide whether a drug can obtain full approval or Conditional Marketing Approval (CMA) (Fig. 1). Unlike the FDA, no dedicated drug application pathway is based only on biomarker efficacy. The CMA requires:

- a favorable benefit-risk profile of the medicinal product in the claimed indication;
- comprehensive post-authorization data within the dossier following a pre-set time frame provided by the applicant;
- an unmet medical need for a seriously debilitating or life-threatening disease which is justified on objective and quantifiable medical or epidemiological information;
- that the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required [3].

Granting of a CMA in Europe 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, when confirmation of the clinical benefits is still required. Biogen® will have to wait for the results of new clinical trials before submitting a new application. These new data may come from the Phase IV confirmatory study (ENVISION trial) requested by the FDA [1]. The company expects results by 2026 [4]. No individual national application is possible for immunotherapies and drugs targeting neurodegenerative diseases in the European Union [5] (Fig. 1).

Regarding other high-clearance anti-amyloid immunotherapies, Eisai® (developing lecanemab) has applied for accelerated approval in the US after the phase II results showing a significant decrease of brain amyloid load together with a significant clinical effect on secondary endpoints [1] (see part 1). On July 5th, 2022, and August 4th, 2022, the FDA formally accepted the company's Biologics Licence Application (BLA) for lecanemab and donanemab, respectively, granting them priority reviews. This means the agency will make a final decision by January 6th, 2023, for lecanemab and by early February 2023, for donanemab [1].

For lecanemab, a phase III clinical trial called Clarity AD is currently running. The readout of this trial will occur in the fall of 2022 [6]. Roche® also started two phase III trials with high-dose subcutaneous gantenerumab (GRADUATE 1 and 2). The trials are slated to run till the end of 2022. Finally, regarding donanemab, the TRAILBLAZER-ALZ 2 study (a phase III clinical

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

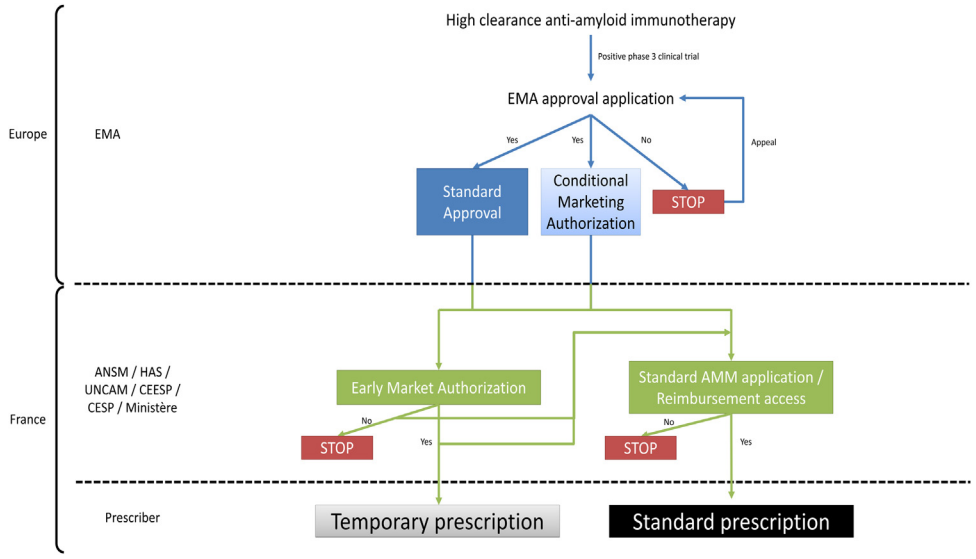

Fig. 1 – Putative scenarios before use in clinical practice in France, in case of positive phase III trial regarding high-clearance anti-amyloid immunotherapy in Alzheimer's disease. EMA = European Medicine Agency, ANSM = *Agence Nationale de Sécurité du Médicament et des produits de santé*, HAS = *Haute Autorité de Santé*, UNCAM = *Union Nationale des Caisses d'Assurance Maladie*, CEESP = *Commission d'Evaluation Economique et de Santé Publique*, CESP = *Comité Economique des Produits de Santé*, AMM = *Autorisation de Mise sur le Marché*, Early Market Authorization = *Autorisation d'Accès Précoce* (AAP).

trial) is ongoing, and its results are expected in mid-2023. Regarding the accelerated approval appliers (Eisai® and Lilly®), if the FDA approves their BLA under the accelerated approval regimen, and if their phase III trials are positive on clinical criteria, this might allow quick market access in the US and essentially limit the restrictions imposed by CMS for coverage of this category of drug. Regarding Europe, to our knowledge, no application to the EMA is undergoing or planned in the short term for these drugs; the companies will probably wait for the results of their phase III trials before any application.

Suppose one of the phase III clinical trials of high-clearance anti-amyloid immunotherapies turns out to be unarguably positive on a clinical primary endpoint with acceptable safety data, and that, in turn, the EMA approves a high-clearance anti-amyloid immunotherapy under a standard approval or a CMA. What could be the following pathway before their use in everyday practice in France? The company may apply to the new French combined *Agence Nationale de Sécurité du Médicament* (ANSM) and *Haute Autorité de Santé* (HAS) procedure for an early approval access (*Autorisation d'Accès Précoce–AAP*) (maximum assessment duration = 3 months) [5]. The two agencies will assess:

- the benefit/risk of the treatment;
- whether it concerns a severe, rare, or disabling disease;
- whether there is a lack of appropriate treatment;
- whether the implementation of treatment is not deferrable;
- whether the new drug is presumed to be innovative (particularly when compared to a possible clinically relevant comparator).

If approved, the drug will be available after a maximum two-month period and automatically reimbursed by the National Medical Insurance (*Assurance Maladie*). After that, a standard application file has to be submitted in the following two years (Fig. 1). From the prescriber's perspective, the new AAP procedure requires four files per patient: (1) the treatment access request form, (2) the treatment initiation form, (3) the follow-up form, and (4) the discontinuation of treatment form.

A standard application for reimbursement after EMA approval would imply the usual pathway for new immunotherapies in France:

- HAS assessment regarding the medical service (*Service Médical Rendu*) and the improvement of the medical service (*Amélioration du Service Médical Rendu*);
- the Commission of Economic Evaluation and Public Health (*Commission d'Evaluation Economique et de Santé Publique* - CEESP) will undoubtedly be called upon to evaluate the medico-economic dimension;
- negotiation and pricing will take place before the Economic Committee for Health Products (*Comité Economique des Produits de Santé*–CESP);
- the public price will be published in the Official Journal;
- The National Union of Health Insurance Funds (*Union Nationale des Caisses d'Assurance Maladie*–UNCAM) will set the reimbursement rate for the drug, and in parallel, a ministerial decree of admission to reimbursement will be published (Fig. 1) [7].

The final registration of this drug on the "*liste en sus*" system, designed to promote access to expensive drugs in French hospitals, may also delay its use in clinical practice. Nevertheless, this procedure will probably be reformed shortly [8]. As a whole, even if the HAS would give a favorable

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

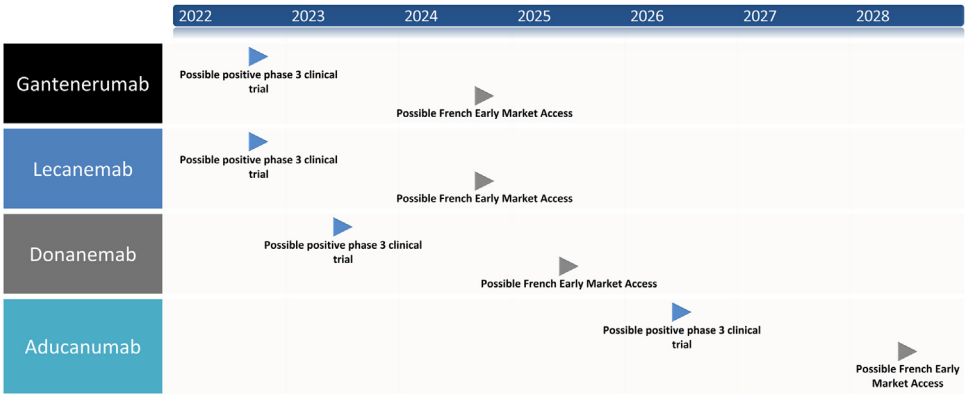

Fig. 2 – Possible timeline for early market access (*Autorisation d'Accès Précoce* - AAP) of high-clearance anti-amyloid immunotherapies close to approval in France in a best-case scenario (i.e., unarguably positive phase III clinical trial on a clinical primary endpoint, EMA approval and French early market access approval).

evaluation regarding the medical service offered by the drug, this procedure could take years, especially when the economic stakes are high, which is likely to be the case for high-clearance anti-amyloid immunotherapies in AD [1].

If the EMA approves a high-clearance anti-amyloid immunotherapy, but if the ANSM/HAS do not approve the AAP, it is likely that high-income patients will attempt to have access to this drug in neighboring European countries, as it has already occurred for anti-CGRP antibodies in migraine [9] or nabiximols in multiple sclerosis [10]. This might cause a dramatic case of two-tier medicine for a common and devastating disease, with potential significant ethical and political consequences.

As detailed in the first part of this review [1], three out of four recent phase II or III clinical trials with high-clearance anti-amyloid immunotherapies have shown a significant effect on clinical outcomes. Five high-clearance anti-amyloid immunotherapies phase III clinical trials in early AD are ongoing (or planned to begin soon) to confirm these results. In all case scenarios, there is a high probability that a high-clearance anti-amyloid immunotherapies phase III trial will be unarguably positive with acceptable safety data before 2025. Therefore, it is very likely that a high-clearance anti-amyloid immunotherapy will obtain EMA approval in the next five years, even if national assurance systems may deem it afterward not suitable for reimbursement. Under the assumption of 1) a phase III clinical trial unarguably positive on a clinical primary endpoint with acceptable safety data, 2) subsequent approval by the EMA, and 3) an early market access authorization in France: a high-clearance anti-amyloid immunotherapy could be temporarily prescribed by French physicians ~2024 for gantenerumab and lecanemab, ~2025 for donanemab, and ~2028 for aducanumab ([1]–Fig. 2). This calculation assumes a ~6-month delay between the disclosure of the phase III results and the formal EMA application, a ~12-month delay for EMA assessment, and a ~6-month delay for the French early market access procedure (including application, assessment by the agencies and delay before availability for the prescribers) (see above).

2. Recommendations for putative use of high-clearance anti-amyloid immunotherapies in France

As underlined in the first part of this review [1], the currently available pooled data from high-dose aducanumab, lecanemab, and donanemab trials, tend to confirm that a significant but slight clinical effect of these drugs emerges in patients with early AD after 18 months. Given the expected disease-modifying property of high-clearance anti-amyloid immunotherapies, it might be reasonable to expect a more significant clinical impact after a long-term follow-up, though this remains to be proven. Besides, safety data analysis confirms that these drugs are responsible for an important risk of ARIA, which can seldom (~1 per 200 treated patients), but beyond chance, be serious and symptomatic with long-term sequelae. If approved by the EMA, and contrary to the FDA notice in the US, such a drug will likely be restricted to the patients meeting the inclusion and exclusion criteria of the positive phase III trials, given its putative high risk/benefit ratio and the emphasis regarding efficacy and safety underlined by the EMA's first review of aducanumab. It will also likely require close monitoring and management of ARIA. Based on the inclusion and exclusion criteria of the ongoing and completed high-clearance anti-amyloid immunotherapies clinical trials [1] and the recommendations from the US neurologists [11,12], we propose the preliminary following recommendations regarding the use of high-clearance anti-amyloid immunotherapies in clinical practice in France in the case of a putative EMA and French approval and reimbursement (Table 1). These recommendations aim to illustrate and help make putative use of high-clearance anti-amyloid immunotherapies practical for French physicians.

2.1. *Patients who could benefit from these therapies (Table 1)*

2.1.1. *Disease Stage*

Patients receiving high-clearance anti-amyloid immunotherapy should be at an early stage of AD, where amyloid is likely

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

Table 1 – Synthetic description of eligible patients for high-clearance anti-amyloid immunotherapies in a real-life setting in case of putative approval in France. Minimum requirements. See text for detail.

AD diagnosis established by	1) Clinical phenotype: amnestic syndrome of the hippocampal type, posterior cortical atrophy, logopenic variant primary progressive aphasia (and uncommon AD phenotypes) 2) Positive biomarkers of AD pathology: A+ (and T +)
Disease stage	Early symptomatic AD with no or low impact on activities of daily living
Age and comorbid conditions	Life expectancy $\geq$ 5 years
Strict contraindications	CAA MRI risk factors of ARIA (i.e., non-CAA comorbid cerebrovascular disease, including $\geq$ 4–5 microbleeds) Antithrombotic drugs* MRI contraindication
Relative contraindications (possible factors increasing the risk of ARIA and/or its severity)	History of ischemic stroke, TIA, high and/or imbalanced cerebrovascular risk factors, autoimmune or inflammatory conditions, seizures, or other disorders associated with extensive white matter pathology
APOE genetic testing	Strongly recommended (for ARIA risk assessment)

A+: positive biomarker of amyloid pathology (low CSF Aβ42, or high CSF Aβ40/42 ratio, or positive amyloid-PET); T+: positive biomarker of tau pathology (high CSF pTau, or positive tau-PET); ARIA: amyloid-related imaging abnormality; TIA: transient ischemic attack; CAA: cerebral amyloid angiopathy. *Whether antithrombotic drugs should be considered as a strict or relative contraindication to high-clearance anti-amyloid immunotherapies will depend on the safety results of the phase III lecanemab and donanemab trials where antithrombotic drugs are allowed.

to have more influence than at the latest stages of the disease [13]. The strict MMSE cut-off ($>$ 20–24) used in the different trials to define early AD is likely to be mentioned in the drugs' notices, analogous to other trials and drugs' notices. Nonetheless, in clinical practice, even if they should be considered in the first place to select eligible patients, they may be disputed in some cases given the well-known influence of education level or instrumental functions impairment (especially language) on this score [14–16]. The donanemab trial proposed a biological selection strategy using amyloid- and tau-PET to estimate pathological disease stages. However, the lack of reimbursement of tau-PET in France and the high cost of two PET examinations per patient, makes this approach unrealistic for large-scale everyday practice to date.

Thus, according to current clinical practice, the definition of early AD should rely on clinical assessment only, but not using a strict and single cognitive test cut-off. Instead, this should be established after an interdisciplinary discussion involving several memory clinic specialists with a particular emphasis on activities of daily living impairment, which should be null or mild, i.e., Clinical Dementia Rating (CDR) scale global score = 0.5 (some patients with CDR = 1 were included in the trials, but few data are available about them). The impact of non-AD-related factors on cognitive and functional tests (e.g., medication, depression, anxiety, comorbidities, etc.) should also be carefully considered.

While clinical trials have established the minimum cognitive performance that a patient must exhibit to be eligible for treatment, the minimum level of impairment justifying starting anti-amyloid immunotherapy is, in fact, unknown. Trials with high-clearance anti-amyloid immunotherapies are being conducted in asymptomatic biomarker-positive individuals (A4 trial – AHEAD 3-45 trial – TRAILBLAZER-ALZ 3 trial – SKYLINE WN42444 trial [1]), but no data are currently available in this population. In this cognitively unimpaired at-risk (a.k.a. preclinical AD) population, prescription of anti-amyloid immunotherapy should not be proposed to date. Indeed, the natural progression to mild cognitive impairment (MCI) and dementia in these patients is usually very slow or non-existent after five years [17]. Therefore, the clinical benefit is unknown for these individuals, but the risk of ARIA is real in these subjects with significant amyloid pathology. Instead, we propose that patients with CDR = 0 be followed up regularly to document a possible decline indicating early treatment with high-clearance anti-amyloid immunotherapies.

2.1.2. *Proof of AD pathology*

Amyloid-β (Aβ) biomarker positivity must be documented before prescribing high-clearance anti-amyloid immunotherapy. Targeting Aβ is more likely to influence symptom evolution if neuropathologically-defined AD is the most probable underlying primary diagnosis than if Aβ is a comorbid pathology of another primary proteinopathy [18]. In this regard, even if not used in completed high-clearance anti-amyloid immunotherapies trials, it might be even more appropriate to restrict the indication of high-clearance anti-amyloid immunotherapies to patients classified as having a 'highly probable' primary diagnosis of AD according to the 2021 recommendations of the International Working Group [18], i.e., with also a positive tau biomarker and either an amnesic, posterior cortical atrophy or logopenic primary progressive aphasia phenotype. Indeed, although clinical trials generally included only amnestic AD phenotypes (CDR memory box = 0.5, RBANS delayed-memory index $<$ 85), there is no reason to believe that non-amnestic MCI due to AD could not benefit from the disease-modifier effect of high-clearance anti-amyloid immunotherapies. This diagnosis should be established after an interdisciplinary discussion. In case of a 'probable', and not 'highly probable', primary diagnosis of AD (i.e., lack of tau biomarker or uncommon AD phenotype with positive amyloid and tau biomarkers), high-clearance anti-amyloid immunotherapy prescription could still be considered, but the risk/benefit ratio is likely to be higher. Therefore, a closer risk assessment should be performed.

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

The recent access to reimbursement of amyloid-PET in France facilitates AD biomarker investigation which no longer relies solely on cerebrospinal fluid (CSF) analysis; and, in turn, the risk that any contraindications to lumbar puncture (i.e., non-stoppable anticoagulants or antiplatelet drugs besides low-dose aspirin, non-treatable coagulation disorder, spinal cord compression, expanding intracranial lesion, and failure to perform lumbar puncture) would have inevitably turned to a contraindication to any high-clearance anti-amyloid immunotherapy. While it is used as an inclusion criterion in the donanemab trial and while it is a unique way to assess tau pathology in individuals with contraindication or failure of lumbar puncture, tau-PET still does not have EMA approval in AD. This could lead to difficulties establishing donanemab's notice after a putative EMA approval, or increasing the AD diagnosis certainty. Given the rapid progression of techniques and knowledge in the field of blood-based biomarkers of AD, both on their diagnostic [19,20] and predictive values [21], it is likely that they will become available in clinical practice in the next few years, either for a formal diagnosis or, more likely, for pre-screening subjects requiring a lumbar puncture or PET examination. This may constitute a game-changer and easier access to biomarker investigations.

2.1.3. *Age limit*

No data currently exist regarding the efficacy and ARIA risk beyond the 50–90 years-old boundaries of the completed high-clearance anti-amyloid immunotherapies trials (with only very few individuals between 85 and 90 years old included in the lecanemab phase II trial). In clinical practice, using a high-clearance anti-amyloid immunotherapy in an early-onset AD patient below 50 years old appears reasonable, given the potential relevance of amyloid pathology in the pathogenesis of early-onset AD [22]. On top of the age limit, the therapeutical decision should be assessed more closely. Two main factors should be considered:

- the prevalence of multiple comorbid proteinopathies (beyond amyloid) and cerebrovascular disease increase with age, suggesting a potential lower benefit of high-clearance anti-amyloid immunotherapies alone for older subjects [23];
- the individual's life expectancy since the expected clinical effect size for these treatments remains slight after an 18-month regimen.

Indeed, a clinically relevant effect would be expected only after five or six years [1]. The mean life expectancy at age 85 is over five years in France, which would justify treating patients at this age [24]. However, in our opinion, any comorbid condition likely to decrease life expectancy (regardless of age) below five years should be considered a strict or relative contraindication. Future post-hoc analyses of clinical trials will need to appropriately address whether age may influence clinical response to anti-amyloid therapies.

2.1.4. *Core ARIA risk factors assessment*

A thorough exclusion criteria assessment should mainly focus on evaluating ARIA risk. As detailed in the first part of this review [1], currently well-established ARIA risks are the *APOE* ε4 status, the number of *APOE* ε4 alleles, baseline microbleeds, high-dose anti-amyloid immunotherapies, and proper pharmacodynamic property of an antibody. Nonetheless, though intuitive, dose lowering should not be considered an option in patients with increased risk of ARIA since these low-dose groups have so far been associated with a lack of clinical effect in clinical trials. The meta-analysis performed in the first part of this review does not suggest any trend for superiority or inferiority of one drug to another so far regarding ARIA risk [1]. Classical cerebrovascular risk factors such as hypertension, hyperlipidemia, and diabetes do not seem to be risk factors for ARIA-E [25–27]. In the case of cerebral amyloid angiopathy (CAA), high-clearance anti-amyloid immunotherapies are so far strongly discouraged since it might be an ARIA-related mechanism or risk factor [28,29]. As a whole, in current clinical practice, the assessment of ARIA risk factors (*APOE* status and the number of ε4 alleles, baseline microbleeds, and CAA) should be individually and carefully discussed in interdisciplinary meetings to guide individual therapeutic decision-making. Testing for *APOE* genotype in clinical practice has been recommended in the 2022 US recommendations since the need for personalized ARIA risk assessment and management appears necessary for high-clearance anti-amyloid immunotherapies, given their high risk/benefit ratio [12]. We also recommend that *APOE* genotyping should be systematically proposed to the patient. Finally, one should remember that other ARIA risk factors might be evidenced in the following years, as current data only come from clinical trials with strict exclusion criteria.

2.1.5. *Other risks assessment*

Beyond these well-established risk factors of ARIA, numerous exclusion criteria were used in high-clearance anti-amyloid immunotherapies trials [1]. Patients with non-AD neurological disorders, history of or recent stroke, and transient ischemic attack (TIA) were systematically excluded. Unstable cardiovascular, systemic conditions, and history of recent cancer were also excluded. Lecanemab, donanemab, and gantenerumab trials excluded individuals with concomitant immunoglobin treatment or under immunosuppressant therapy. Impaired renal or liver function was an exclusion criterion in aducanumab and donanemab trials. Bleeding disorders were excluded in half trials (aducanumab and gantenerumab). Any unstable psychiatric disease was also mostly unanimously considered as an exclusion criterion. Finally, the lack of a reliable informant or care partner was also an exclusion criterion. A strict application of these criteria would lead to numerous exclusions in clinical practice [30]. Considering the lack of data regarding high-clearance anti-amyloid immunotherapy in these disorders, no clear guidance can be recommended so far, and the risk/benefit ratio should be carefully discussed in interdisciplinary meetings. Besides, history of ischemic stroke, TIA, age, hypertension, smoking, intensity of anticoagulation, and poor balance are well-known risk factors for intracranial hemorrhage. They should be thoroughly considered since they might be risk factors either for ARIA-H itself but also for ARIA-H severity [27,31,32]. The updated US recommendations also underline the importance of detecting past medical conditions that may predispose to ARIA or increase the likelihood of ARIA complications,

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

including autoimmune or inflammatory conditions, seizures, or other disorders associated with extensive white matter pathology [12]. These factors are likely not to be regarded as strict exclusion criteria. Still, their careful assessment should be balanced with the core ARIA risk factors (see above) before prescribing anti-amyloid immunotherapy. Evaluation of the potential correct compliance of the patient regarding anti-amyloid immunotherapy will also be likely to be considered before prescribing these long-term recurrent infusion treatments with close MRI monitoring. Finally, no data regarding high-clearance anti-amyloid immunotherapies neutralizing antibodies have so far been disclosed, but this might have to be considered in the future.

2.1.6. *Baseline magnetic resonance imaging (MRI)*

In line with sections 2.1.5 and 2.1.6, and as detailed in Table 2 from the first part of this review [1], baseline MRI exclusion criteria were also strict in all high-clearance anti-amyloid immunotherapies trials: acute or subacute hemorrhage, macrohemorrhage, greater than four or five microhemorrhages, large cortical infarction, more than one lacunar infarction, superficial siderosis, or diffuse white matter disease were most of the time excluded. All these abnormalities are either well-established risk factors of ARIA, markers of CAA according to Boston criteria 2.0 [33], or general risk factors for intracranial hemorrhage. In the lack of data regarding high-clearance anti-amyloid immunotherapies use in patients with any of these MRI abnormalities and the high likelihood that they might increase the ARIA risk or its severity, these MRI lesions should be considered strict exclusion criteria. In line with the US recommendations, a patient with a contraindication for MRI should not benefit from anti-amyloid immunotherapy since it would prevent this baseline assessment and close MRI monitoring.

2.1.7. *Other medications*

Anticoagulants and antiplatelet therapies (besides low-dose aspirin) are identified risk factors of ARIA-H [34] and were excluded from the aducanumab trials and the ongoing gantenerumab trials [1]. Nonetheless, they were allowed in the ongoing donanemab and lecanemab trials. In the absence of currently available data, these antithrombotic medications should be considered as strict contra-indications to any anti-amyloid immunotherapy, but this might change according to the future safety results of the donanemab and lecanemab phase III trials. Patients under cholinesterase inhibitors and memantine were allowed during any high-clearance anti-amyloid immunotherapy trial. This should not be considered as an exclusion criterion. Furthermore, the association of drugs with very distinct pharmacodynamic effects might be beneficial.

2.2. *How many patients could/should benefit from these therapies?*

According to recent French epidemiological estimates, about 274,000 patients in France suffer from amyloid-positive mild AD and 1.6 million from amyloid-positive MCI [35]. This is in line with the global estimation of the prevalence of amyloid-positive prodromal AD population [36], applied to the 2022 French population (https://population.un.org/wpp/DataQuery/): 1,470,258 individuals (933,165–2,250,573) (Fig. 3). Anderson et al. [30] estimated the percentage of patients fulfilling the exclusion criteria from the aducanumab phase III trials from the US Medicare data. 92.2% of patients with AD related-disorders, 91.0% with AD (without information regarding the stage), and 85.5% with MCI met at least one trial exclusion criteria. This calculation is difficult to apply to the putative 1.9 million amyloid-positive mild AD or MCI French individuals. Indeed, Anderson et al. used the strict exclusion criteria of the aducanumab trials, i.e., excluding any 'cardiovascular disease' which is more prevalent in the US population

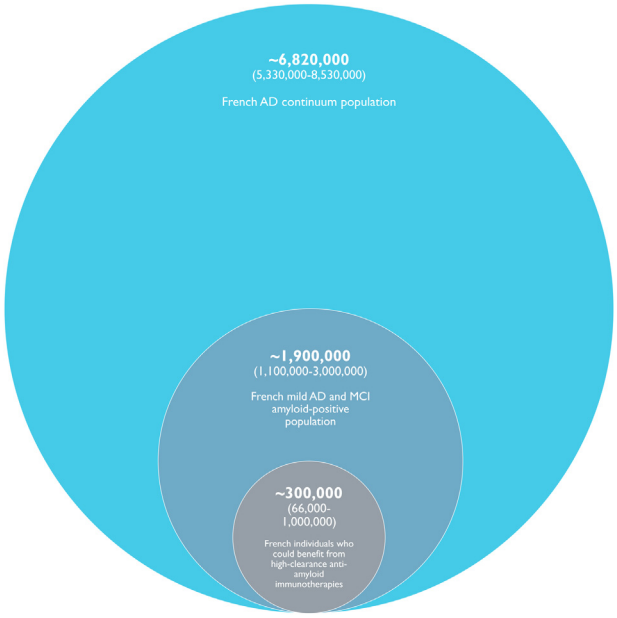

Fig. 3 – Rough estimate of the number of French patients potentially eligible for high-clearance anti-amyloid immunotherapies considering the current inclusion and exclusion criteria of terminated or close-to-end phase III clinical trials. Prevalence of amyloid-positive individuals according to each stage of the disease [35,36], applied to the French population (https://population.un.org/wpp/). Estimates of individuals with contraindications based on American and Italian cohorts considering the contraindications from the aducanumab's trials [30,37,38]. The French AD continuum population (large light blue circle) corresponds to the amyloid-positive asymptomatic-at-risk (a.k.a. preclinical) (~4,630,000), prodromal (~1,470,000), and demented (~720.000) AD population. The intermediate dark blue circle corresponds to the French mild AD and MCI amyloid-positive population (=current targeted AD stage of high-clearance anti-amyloid immunotherapies closest to approval). The small gray circle corresponds to the French mild AD and MCI amyloid-positive population without exclusion criteria (i.e., individuals who could fulfill both inclusion and exclusion criteria of high-clearance anti-amyloid immunotherapies, and be under these drugs, in case of approval).

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

than in France, and did not apply a strict 'highly probable' definition of AD using biomarkers and specific phenotypes as it may likely be used in clinical practice. In two Italian geriatric centers, the proportion of patients eligible for aducanumab was estimated to be ~6–33% of mild AD or MCI populations. Still, the proportion of patients without significant amyloid pathology after a biomarker investigation was included in this calculation of eligibility proportion [37,38]. As a whole, one can reasonably estimate that even under a pessimistic scenario, more than 66,000 patients in France (and more likely ~300,000 and up to 1 million) could be eligible for a high-clearance anti-amyloid immunotherapy in case of approval.

3. Possible lines of approach for practical implementation of anti-amyloid therapies in France

3.1. *Who should decide and initiate an anti-amyloid prescription?*

These drugs' high risk/benefit ratio inevitably implies a highly specialized diagnostic and a thorough exclusion criteria assessment. Thus, the initial prescription of these drugs should be done in specialized memory clinics/tertiary centers. In France, this appears to be currently only possible in *Centres Mémoire de Ressources et de Recherche* (CMRR) or memory clinics with access to biomarker investigation and expert neuroradiologists to organize interdisciplinary meetings as already implemented in oncology or for the decision for second-line immunotherapy in multiple sclerosis for instance. These interdisciplinary meetings should involve at least one physician specialized in cognitive disorders, one radiologist, and one neuropsychologist.

The current limited resources of these tertiary centers in France will likely be the major initial limiting factor for a high-clearance anti-amyloid immunotherapy prescription. In the case of a definite approval for one of these drugs, the need to develop these structures will be very high. Besides, the opportunity of a potential 'disease-modifying' drug aimed at early AD will likely increase the need for a specialized diagnosis of early-stage AD (involving specialized neuropsychological assessment, blood testing, MRI, PET, CSF biomarkers investigations), increasing the activity of these memory clinics. This increased activity is challenging to estimate but is likely to be very high. Between 2014 and 2018, the rate of CSF biomarker use for AD diagnosis varied only from 2.1% to 6.7% in French memory clinics. [39]. This meager figure allows an estimation of the putative increase of activity for biomarker investigation necessary in case of an approval of high-clearance anti-amyloid immunotherapy (not mentioning the increased need for consultation, since ~30–50% of dementia remains currently undiagnosed in France [40,41]). To this prospect, the role of primary care physicians will be of paramount importance, and screening strategies for general practitioners have already been jointly published by the *Fédération des Centres Mémoires* and the *Collège de Médecine Générale* [42]. The role of primary care physicians in this screening will increase. However, the need for confirmatory biomarker investigation, psychometric tests, and careful assessment of contraindications will still rely on specialists. Even in the case of a putative validation of amyloid and tau plasma biomarkers in the future, that could be used in a first-line biomarker screening strategy, the need for a specialized clinical, neuropsychological, radiological, and CSF and/or PET biomarker assessment before an interdisciplinary meeting aimed to discuss an individual high-clearance anti-amyloid immunotherapy indication will remain.

3.2. *How and where should anti-amyloid infusions be delivered?*

High-clearance anti-amyloid immunotherapies will likely be restricted prescriptions for limited use in a hospital, at least for the first infusion and under a temporary prescription regimen. Nonetheless, the critical number of patients under a monthly infusion (even bi-weekly for lecanemab or weekly for gantenerumab as currently being assessed in the phase II GRADUATION trial) will exceed the entire French neurological and geriatric daily hospital unit capacity. How long AD patients should remain under a high-clearance anti-amyloid immunotherapy, if well tolerated, is currently completely unknown. The donanemab trial proposes an 'induction' approach where infusions are stopped after the amyloid-PET turns negative, which might partially alleviate the health care system. Still, no long-term data are currently available to confirm the validity of such an approach. Besides, proper pharmacodynamic properties of donanemab may complexify the application of such a scheme to other high-clearance anti-amyloid immunotherapies: donanemab targets only the insoluble aggregated forms of Aβ, unlike the other high-clearance anti-amyloid immunotherapies that can also target toxic Aβ oligomers (oligomers cannot be imaged with amyloid-PET). Only a home-based self-infusion model appears viable for large-scale and long-term use in every scenario, as it is already starting to be the case in multiple sclerosis immunotherapies. In this regard, the subcutaneous formulation of gantenerumab, with a user-friendly self-injection device and training, may be an interesting option. The other companies are also developing such formulations, with phase I studies of subcutaneous lecanemab, donanemab, and aducanumab underway. The model of infusion centers, which already exists in the US, might also be a solution, similar to what already exists in France for dialysis centers.

The action list in case of putative high-clearance anti-amyloid immunotherapy approval and use in clinical practice is summarized in Table 2.

4. Monitoring of patients under anti-amyloid immunotherapies

Close MRI monitoring for ARIA detection was performed in all high-clearance anti-amyloid immunotherapy trials. For example, seven MRIs were performed to monitor the 18-month treatment duration in the aducanumab phase III trials. This allowed for dose adjustment and personalized titration. The FDA notice regarding aducanumab in clinical practice only recommends two MRIs (before the seventh and twelfth infusions). The US experts recommend two additional MRIs

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

Table 2 – Action list in case of high-clearance anti-amyloid immunotherapy approval in France.

	Early and temporary access	Standard Approval
Indication and contraindication assessment	Creation of interdisciplinary meetings (involving at least one physician specialized in cognitive disorders, one radiologist, and one neuropsychologist) that should ideally take place in CMRR	Creation of interdisciplinary meetings (involving at least one physician specialized in cognitive disorders, one radiologist, and one neuropsychologist) that should ideally take place in CMRR
Formal AD biomarker investigation before a prescription discussion	*CSF and/or amyloid PET–standard procedure*	Agencies should discuss approval and reimbursement of tau-PET tracer to comply with some high-clearance anti-amyloid immunotherapies' (donanemab) inclusion criteria, and to allow for tau biomarker assessment in patients with contra-indication or failure of the lumbar puncture procedure
ARIA monitoring	Training of specialized centers radiologists Definition of standardized imaging protocols Dedicated and programmed MRI slots for every patient under high-clearance anti-amyloid immunotherapy	National training program for radiologists Definition of standardized imaging protocols Dedicated and programmed MRI slots for every patient under high-clearance anti-amyloid immunotherapy
	Follow-up by the prescriber using a standardized procedure (alert for abnormal MRI and dose adaptation or drug discontinuation formalized)	Combined follow-up by an advanced practice nurse and the prescriber using a standardized procedure (alert for abnormal MRI and dose adaptation or drug discontinuation formalized)
	Definition of emergency procedures and healthcare circuits for serious ARIA	Definition of emergency procedures and healthcare circuits for serious ARIA
Drug delivery	Will depend on the drug agencies' decision–ideally, combined hospital and community care prescription (a prescription restricted to hospitals and expert centers will quickly exceed their capacities and will be a limiting factor to drug access)	Will depend on the drug agencies' decision–but the expected number of patients will by far exceed current expert centers' and hospitals' capacities–ideally, combined hospital and community care prescription
		If home-perfusion is approved: increased need for home-based nurse care (in the case of self-injection device: the increased need for home-based nurse care is partially alleviated but still necessary for the initiation, and for patients/caregivers who are not able to use the device) Discuss the creation of 'infusion centers' as in the US
Patient information	Oral and ideally written information–Care support person highly recommended	Oral and ideally written information–Care support person highly recommended
Memory Clinics	Increase of diagnostic and follow-up activity–Number of centers and physicians will limit the prescription	Need for a significant increase in the number of Memory Clinics to allow for generalized access to an early biologically-proven AD diagnosis
	Reinforcement of networks between CMRR and non-CMRR Memory Clinics to provide easy access to the interdisciplinary meetings	Creation of Memory Clinics–Community Care networks
	Improved access to biomarker investigations in non-CMRR Memory Clinics	Establish new diagnostic procedures for the general population screening and formal diagnosis of AD, for wider access for the French population to an early-stage biomarker-proven AD diagnosis

(before the fifth and ninth infusions) and to perform an MRI at the occurrence of an unspecific symptom suggestive of ARIA (headache, vomiting and/or nausea, confusion, dizziness, visual disturbance, gait difficulties, loss of coordination, tremor, transient ischemic attack, new-onset seizures, or significant and unexpected acute cognitive decline) [11,12]. MRI monitoring similar to what the US experts recommend is likely the most appropriate in the French healthcare system. The company will likely establish discontinuation and suspension protocols, which will evolve with time and use of these drugs. The current version of the aducanumab protocol, proposed by the US expert panel, proposes a protocol suspension for every symptomatic ARIA or for any asymptomatic moderate or severe radiologic ARIA (the severity being established by its size) and to resume the treatment after ARIA resolution (according to the duration of treatment suspension, titration can be restarted from zero). For the most severe symptomatic cases of ARIA, in line with CAA-related inflammation management, they recommend beginning high-dose glucocorticoid therapy for five days followed by oral treatment slowly tapered over weeks or months [12]. Any additional symptomatic treatment, such as anticonvulsant therapy, should also be considered if necessary. Definitive suspension of treatment is recommended for any of the following cases: any macrohemorrhage, more than one area of superficial siderosis, more than ten microhemorrhages occurring since initiation therapy, more than two episodes of ARIA, severe symptoms of ARIA, development of any medical condition that requires anticoagulation (e.g., atrial fibrillation, deep vein thrombosis, pulmonary embolism, hypercoagulable state) [12].

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

In case of a definite approval, radiologists' essential role in ARIA monitoring will require an initiative from the French Society of Neuroradiology (*Société Française de NeuroRadiologie* – SFNR) to homogenize the MRI sequences [43] and raise awareness of the radiologists to ARIA detection and staging (since mild ARIA-E can easily go unnoticed by an untrained physician) [27]. Close clinical monitoring will also inevitably increase the medical time, primarily if the infusion is not performed in a specialized center which is the most likely scenario (see above). This could be partially overcome by recruiting advanced practice nurses (*Infirmières de Pratique Avancée*, equivalent to clinical nurse specialists in Canada) in CMRR who could help with the close monitoring of patients under anti-amyloid therapies in line with primary care physicians, radiologists, and the referent specialist. Finally, it is important to underline that most ARIAs occurred during the first twelve months of treatment in the aducanumab trials [44]. Hence, a long-term close MRI monitoring of ARIA is likely not necessary for patients under treatment. The action list in case of putative high-clearance anti-amyloid immunotherapy approval and use in clinical practice is summarized in Table 2.

5. Ethical considerations

Approval of high-clearance anti-amyloid immunotherapy would be a game-changer for patients and the French healthcare system. Beyond the medico-economical and the public health considerations, and above the physicians' role, the current controversy in the US illustrates that individual prescribers are likely to have a different opinion regarding the efficacy and risk of these drugs despite an agency's decision. In the US, in a recent survey of 74 neurologists by the market research firm Spherix Global Insight, 84% said they had lost confidence in the FDA over the year 2021, partly due to the agency's aducanumab decision. Still, two-thirds expected to treat some patients with the antibody, suggesting usage might pick up if covered [45].

In France, in case of such a controversy, it should be recalled that since the 2002 law n°2002-303 on patients' rights and the quality of the healthcare system (''Loi Kouchner''), the patient is the decision-maker for any medical decision regarding his/her condition:

> ''Art. L. 1111-4.–Any person makes, with the health professional and taking into account the information and recommendations that he or she provides, decisions concerning his or her health.''
> ''The doctor must respect the person's wishes after informing him or her of the consequences of his or her choices. [...]''
> ''No medical act or treatment may be performed without the free and informed consent of the person, and this consent may be withdrawn at any time.''

On the other hand, the code of medical ethics (*Code de déontologie*) also provides the liberty of prescription:

> ''Article 8 (article R.4127- 8 of the public health code):On the other hand, the code of medical ethics (*Code de déontologie*) also provides the liberty of prescription:
> ''Within limits fixed by the law and considering the acquired data of science, the doctor can prescribe what he thinks the most appropriate in the circumstances.''
> ''Without neglecting his duty of moral assistance, he must limit his prescriptions and acts to what is necessary for the care's quality, safety, and effectiveness.''
> ''He must consider the advantages, disadvantages, and consequences of the various possible investigations and therapies.''

Together, these law articles remind us that, if approved by the agencies, whatever the personal opinion of the prescriber regarding these drugs, he/she will have to consider it, and inform the patient of the existence of these drugs, their advantages, disadvantages, and consequences. Given the strong individual influence that a physician can have on the patient's decision according to how he/she informs his/her patient [46], we recommend that the possible therapeutic options proposed to the patient be discussed not individually but collectively within interdisciplinary meetings. Given the high risk/benefit ratio of these drugs and the impact of the disease on cognitive functions, a particular emphasis should be made on ensuring the patients' understanding and consent [47]. This raises the issue of cognitive disorders and consent specific to this population of AD patients and emphasizes the role of the 'support person' (*personne de confiance*).

6. Conclusion

Despite the recent European refusal of aducanumab approval, there is a high probability that a high-clearance anti-amyloid immunotherapy phase III trial will turn out to be positive with acceptable safety data and may, in turn, obtain approval from the EMA in the upcoming five years. Beyond controversies regarding the actual efficacy of these drugs, current data suggest that the risk/benefit ratio is likely to be high after an 18-month treatment. Besides, the number of patients potentially affected by this decision in France will likely be hundreds of thousands. It will push to modify the current organization of French Memory Clinics. If such a decision occurs in the upcoming years, Memory Centers' physicians should be ready to handle these changes quickly since temporary use could be proposed before the definite approval and reimbursement procedures (as soon as 2024 for early market access of lecanemab and gantenerumab in France). We suggest that therapeutic decisions should be made collectively within specialized interdisciplinary meetings where a thorough individual assessment of indications and contraindications can be made. In case of definite approval of a high-clearance anti-amyloid immunotherapy by the drug agencies, home infusions (preferably with self-injection devices), will likely be the only viable solution for large-scale and long-term use of these drugs. An imaging monitoring protocol should be quickly established in line with radiologists. Close clinical follow-up should involve advanced practice nurses. Finally, definite approval would also affect significant changes in the means and organization of AD care networks, in line with primary care physicians and Memory Clinics, to provide wider access for the French population to an early-stage biomarker-

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

proven AD diagnosis; the prerequisite for high-clearance anti-amyloid immunotherapy access.

Disclosure of interest

Independent of this work, NV received research support from *Fondation Bettencourt-Schueller*, *Fondation Servier*, *Union Nationale pour les Intérêts de la Médecine* (UNIM), *Fondation Claude Pompidou*, *Fondation Alzheimer*, and *Fondation pour la Recherche sur l'Alzheimer*; travel grant from the Movement Disorders Society, Merz-Pharma and GE Healthcare SAS; is an unpaid local principal investigator or sub-investigator in NCT04241068 (aducanumab, Biogen), NCT04437511 (donanemab, Eli-Lilly), NCT05463731 (remternetug, Eli-Lilly), NCT04592341 (gantenerumab, Roche), NCT03887455 (lecanemab, Eisai), NCT03352557 (gosuranemab, Biogen), NCT03828747 and NCT03289143 (semorinemab, Roche), NCT04619420 (JNJ-63733657, Janssen–Johnson & Johnson), NCT04374136 (AL001, Alector), NCT04592874 (AL002, Alector), NCT04867616 (bepranemab, UCB Pharma), NCT04777396 and NCT04777409 (semaglutide, Novo Nordisk); and has given unpaid lectures in symposia organized by Eisai and the Servier Foundation.

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 funding, not including pharmaceutical companies or foundations supported by pharmaceutical companies.

REFERENCES

[1] Villain N, Planche V, Levy R. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 1: Meta-analysis and review of efficacy and safety data, and medico-economical aspects. Rev Neurol (Paris) 2022. http://dx.doi.org/10.1016/j.neurol.2022.06.012. In press.
[2] Aduhelm: Pending EC decision | European Medicines Agency n.d. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/aduhelm (accessed January 18, 2022).
[3] Nisticò R, Borg JJ. Aducanumab for Alzheimer's disease: a regulatory perspective. Pharmacol Res 2021;171:2–4. http://dx.doi.org/10.1016/j.phrs.2021.105754.
[4] Update on the Phase 4 Confirmatory Study of ADUHELM® | Biogen n.d. https://investors.biogen.com/news-releases/news-release-details/update-phase-4-confirmatory-study-aduhelmr (accessed January 17, 2022).
[5] Autorisation de mise sur le marché pour les médicaments - ANSM n.d. https://ansm.sante.fr/page/autorisation-de-mise-sur-le-marche-pour-les-medicaments (accessed January 25, 2022).
[6] EISAI statement on the Centers for Medicare and Medicaid services' national coverage determination with coverage with evidence development for monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease | News Release: 2022 | Eisai Co., Ltd. n.d. https://ww.eisai.com/news/2022/news202226.html (accessed April 25, 2022).
[7] Médicaments innovants : consolider le modèle français d'accès précoce - Sénat n.d. https://ww.senat.fr/notice-rapport/2017/r17-569-notice.html (accessed January 25, 2022).
[8] Innovation Santé 2030 - Ministère des Solidarités et de la Santé n.d. https://solidarites-sante.gouv.fr/actualites/presse/dossiers-de-presse/article/innovation-sante-2030 (accessed January 25, 2022).
[9] Migraines sévères : ce traitement innovant dont la France ne veut pas | Slate.fr n.d. http://www.slate.fr/story/205520/migraines-severes-traitement-innovant-anticorps-monoclonaux-maladie-douleurs (accessed January 25, 2022).
[10] Médicaments : ils vont à l'étranger pour se faire soigner - Le Parisien n.d. https://www.leparisien.fr/archives/je-ne-me-sens-pas-comme-une-delinquante-05-04-2016-5686925.php (accessed January 25, 2022).
[11] Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: appropriate use recommendations. J Prev Alzheimer's Dis 2021;8:398–410. http://dx.doi.org/10.14283/JPAD.2021.41.
[12] Cummings J, Rabinovici GD, Atri A, Aisen P, Apostolova LG, Hendrix S, et al. Aducanumab: appropriate use recommendations update. J Prev Alzheimer's Dis 2022;9:221–30. http://dx.doi.org/10.14283/JPAD.2022.34.
[13] Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. Arch Neurol 2011;68:1062–4. http://dx.doi.org/10.1001/ARCHNEUROL.2011.70.
[14] Kalafat M, Hugonot-Diener L, Poitrenaud J. Standardisation et étalonnage français du "Mini Mental State" (MMS) version GRÉCO. [French standardization and range for the GRECO version of the "Mini Mental State" (MMS).]. Rev Neuropsychol 2003;13:209–36.
[15] Wu Y, Zhang Y, Yuan X, Guo J, Gao X. Influence of education level on MMSE and MoCA scores of elderly inpatients. Appl Neuropsychol Adult 2021. http://dx.doi.org/10.1080/23279095.2021.1952588.
[16] Vigliecca NS, Pealva MC, Molina SC, Voos JA, Vigliecca MR. Is the Folstein's Mini-Mental test an aphasia test? Appl Neuropsychol Adult 2012;19:221–8. http://dx.doi.org/10.1080/09084282.2011.643962.
[17] Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimer's Dement 2018;14:981–8. http://dx.doi.org/10.1016/j.jalz.2018.03.005.
[18] Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol 2021;20:484–96. http://dx.doi.org/10.1016/s1474-4422(21)00066-1.
[19] Thijssen E, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med 2020;26:387–97. http://dx.doi.org/10.1038/s41591-020-0762-2.
[20] Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs other neurodegenerative disorders. JAMA - J Am Med Assoc 2020;324:772–81. http://dx.doi.org/10.1001/jama.2020.12134.
[21] Palmqvist S, Tideman P, Cullen N, Zetterberg H, Blennow K, Dage JL, et al. Prediction of future Alzheimer's disease

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002

dementia using plasma phospho-tau combined with other accessible measures. Nat Med 2021;27:1034–42. http://dx.doi.org/10.1038/s41591-021-01348-z.
[22] Frisoni GB, Altomare D, Thal DR, Ribaldi F, van der Kant R, Ossenkoppele R, et al. The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. Nat Rev Neurosci 2022;23(1):53–66. http://dx.doi.org/10.1038/s41583-021-00533-w.
[23] Spina S, La Joie R, Petersen C, Nolan AL, Cuevas D, Cosme C, et al. Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease. Brain 2021;144:2186–98. http://dx.doi.org/10.1093/BRAIN/AWAB099.
[24] Crimmins EM, Solé-Auró A. Life expectancy, health, and functioning among the 85-Plus population in Europe and the United States. Public Policy Aging Rep 2013;23:3–9. http://dx.doi.org/10.1093/PPAR/23.2.3.
[25] Brashear HR, Ketter N, Bogert J, Di J, Salloway SP, Sperling R. Clinical evaluation of amyloid-related imaging abnormalities in Bapineuzumab Phase III studies. J Alzheimer's Dis 2018;66:1409–24. http://dx.doi.org/10.3233/JAD-180675.
[26] Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways. Nat Rev Neurol 2020;16:30–42. http://dx.doi.org/10.1038/s41582-019-0281-2.
[27] Barakos J, Purcell D, Suhy J, Chalkias S, Burkett P, Grassi CM, et al. Detection and management of amyloid-related imaging abnormalities in patients with Alzheimer's Disease treated with anti-amyloid beta therapy. J Prev Alzheimer's Dis 2022;2:211–20. http://dx.doi.org/10.14283/jpad.2022.21.
[28] Greenberg SM, Cordonnier C, Schneider JA, Smith EE, van Buchem MA, van Veluw SJ, et al. Off-label use of aducanumab for cerebral amyloid angiopathy. Lancet Neurol 2021;20:596–7. http://dx.doi.org/10.1016/S1474-4422(21)00213-1.
[29] Sveikata L, Charidimou A, Viswanathan A. Vessels sing their ARIAs: the role of vascular amyloid in the age of aducanumab. Stroke 2022;53:298–302. http://dx.doi.org/10.1161/STROKEAHA.121.036873.
[30] Anderson TS, Ayanian JZ, Souza J, Landon BE. Representativeness of participants eligible to be enrolled in clinical trials of aducanumab for Alzheimer Disease compared with medicare beneficiaries with Alzheimer Disease and mild cognitive impairment. JAMA 2021;326:1627–9. http://dx.doi.org/10.1001/JAMA.2021.15286.
[31] Ögren J, Irewall AL, Söderström L, Mooe T. Serious hemorrhages after ischemic stroke or TIA–Incidence, mortality, and predictors. PLoS One 2018;13:e0195324. http://dx.doi.org/10.1371/JOURNAL.PONE.0195324.
[32] Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, et al. Major risk factors for intracerebral hemorrhage in the young are modifiable. Stroke 2005;36:1881–5. http://dx.doi.org/10.1161/01.STR.0000177480.62341.6B.
[33] Charidimou A, Boulouis G, Frosch MP, Baron J, Pasi M, Albucher JF, et al. The Boston criteria version 2. 0 for cerebral amyloid angiopathy : a multicentre, retrospective, MRI–neuropathology diagnostic accuracy study; 2022;21. http://dx.doi.org/10.1016/S1474-4422(22)00208-3.
[34] Arrighi HM, Barakos J, Barkhof F, Tampieri D, Jack CJr, Melançon D, et al. Amyloid-related imaging abnormalities-haemosiderin (ARIA-H) in patients with Alzheimer's disease treated with bapineuzumab: a historical, prospective secondary analysis. J Neurol Neurosurg Psychiatry 2016;87(1):106–12. http://dx.doi.org/10.1136/jnnp-2014-309493.
[35] Dufouil C. Maladie d'Alzheimer : quels impacts ? Rencontres Francoph. sur la Mal. d'Alzheimer les Syndr. Apparent., Marseille;. 2021.
[36] Gustavsson A, Norton N, Fast T, Frölich L, Georges J, Holzapfel D, et al. Global estimates on the number of persons across the Alzheimer's disease continuum; 2022;1–13. http://dx.doi.org/10.1002/alz.12694.
[37] Padovani A, Caratozzolo S, Rozzini L, Pilotto A, Benussi A, Tedeschi G. ''Real-world'' eligibility for aducanumab depends on clinical setting and patients' journey. J Am Geriatr Soc 2021;8–10. http://dx.doi.org/10.1111/jgs.17530.
[38] Canevelli M, Rossi PD, Astrone P, Consorti E, Vanacore N, Cesari M. Real world'' eligibility for aducanumab. J Am Geriatr Soc 2021;69:2995–8. http://dx.doi.org/10.1111/jgs.17390.
[39] Epelbaum S, Paquet C, Hugon J, Dumurgier J, Wallon D, Hannequin D, et al. How many patients are eligible for disease-modifying treatment in Alzheimer's disease?. A French national observational study over 5 years. BMJ Open 2019;9:1–11. http://dx.doi.org/10.1136/bmjopen-2019-029663.
[40] Maladie d'Alzheimer et autres démences n.d. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-neurodegeneratives/maladie-d-alzheimer-et-autres-demences/donnees/#tabs (accessed January 27, 2022).
[41] Observatoire Cap Retraite. La France face à la prise en charge de la maladie d'Alzheimer 2015. https://www.capretraite.fr/wp-content/uploads/2016/04/synthese-observatoire-alzheimer.pdf (accessed January 27, 2022).
[42] Krolak-Salmon P, Letrilliart L, Ceccaldi M, Andrieu S, Guérin O, Dubois B, et al. Vers une stratégie nationale de diagnostic des troubles cognitifs. Approche commune du Collège de médecine générale et des spécialistes des troubles neurocognitifs. Press Med 2018;47:75–83. http://dx.doi.org/10.1016/j.lpm.2017.10.029.
[43] Sperling RA, Jack CRJ, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimer's Dement J Alzheimer's Assoc 2011;7:367–85. http://dx.doi.org/10.1016/j.jalz.2011.05.2351.
[44] Salloway S, Chalkias S, Barkhof F, Burkett P, Barakos J, Purcell D, et al. Amyloid-related imaging abnormalities in 2 Phase 3 Studies evaluating aducanumab in patients with early Alzheimer Disease. JAMA Neurol 2021;02142. http://dx.doi.org/10.1001/jamaneurol.2021.4161.
[45] Two-thirds of neurologists expect to start some patients on Aduhelm next year: survey - Clinical Daily News - McKnight's Long-Term Care News n.d. https://www.mcknights.com/news/clinical-news/two-thirds-of-neurologists-expect-to-start-some-patients-on-aduhelm-next-year-survey/ (accessed January 26, 2022).
[46] Bomhof-Roordink H, Gärtner FR, Stiggelbout AM, Pieterse AH. Key components of shared decision making models: a systematic review. BMJ Open 2019;9. http://dx.doi.org/10.1136/BMJOPEN-2019-031763.
[47] Chiong W, Tolchin BD, Bonnie RJ, Busl KM, Cruz-Flores S, Epstein LG, et al. Decisions with patients and families regarding aducanumab in Alzheimer Disease, with recommendations for consent. Neurology 2022;98:154–9. http://dx.doi.org/10.1212/wnl.0000000000013053.

Please cite this article in press as: Villain N, et al. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. Revue neurologique (2022), https://doi.org/10.1016/j.neurol.2022.08.002