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## Review

## Lecanemab for early Alzheimer's disease: Appropriate use recommendations from the French federation of memory clinics

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## ABSTRACT

Lecanemab, a monoclonal antibody targeting  $\beta$ -amyloid protofibrils, has shown promising results in a Phase III clinical trial for the treatment of early stages of Alzheimer's disease (AD) and has been approved by the European Medicines Agency. An Early Market Authorization could be submitted to the French regulatory agencies, potentially allowing for the drug's use in clinical practice in France in 2025.

To guide French clinicians in administering lecanemab in a standardized way, the French Federation of Memory Clinics has developed appropriate use recommendations for lecanemab that highlight relevant questions established to ensure an optimal risk-benefit ratio.

The recommendations emphasize that lecanemab treatment requires a comprehensive individualized evaluation of the risk-benefit ratio, which should occur in multidisciplinary meetings. When approved, the guidelines support the use of blood biomarkers, proposing specific cutoffs for patients eligible for lecanemab under restricted conditions. In addition to the European Medicines Agency restrictions in patients on anticoagulants, and *APOE4* homozygotes, the guidelines recommend against lecanemab treatment for patients with high amyloid-related hemorrhagic risk such as probable cerebral amyloid angiopathy (Boston criteria v1.5) until further data become available. Additionally, we recommend that MRI monitoring be started before the third infusion to account for early Amyloid Related Imaging Abnormalities (ARIA) occurring on lecanemab. It is recommended to establish a specific clinical care pathway with protocols for patients with ARIA, with trained physicians and radiologists with expertise in neurological emergency and intensive care. Finally, a discontinuation protocol based on dementia severity assessment after 18 months of lecanemab treatment is suggested.

Access to lecanemab requires a personalized biological and genetic diagnosis of AD, which is currently not necessary in most cases. Therefore, the healthcare system must rapidly adjust to new diagnostic procedures and treatment delivery to ensure equal access for all individuals.

## 1. Introduction

In 2023, lecanemab, a humanized IgG1 monoclonal antibody with high selectivity for  $\beta$ -amyloid oligomers and protofibrils, showed

promising results in a Phase III clinical trial for the treatment of early Alzheimer's disease (AD) [1]. After 18-month follow-up, it slowed cognitive decline by 27 % on the primary endpoint, Clinical Dementia Rating-Sum of Boxes (CDR-SB), and met all secondary clinical endpoints

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[2]. It was granted marketing authorization by the EMA in November 2024 with restriction to patients who have only one or no copy of Apolipoprotein E  $\epsilon$ 4 allele (*APOE4*) and who are not on anticoagulants. An Early Market Authorization (*Autorisation d'Accès Précoce - AAP*) could be submitted to the French regulatory agencies *ANSM* (*Agence Nationale de Sécurité du Médicament et des produits de santé* - French Agency for the Safety of Medicines and Health Products) and *HAS* (*Haute Autorité de Santé* - French Health Authority). If approved, this could allow for lecanemab to be used in clinical practice in France in 2025 [3].

In the CLARITY-AD trial, stringent inclusion and exclusion criteria were applied to identify early AD patients, ensuring the selection of suitable candidates and minimizing adverse events, such as Amyloid-Related Imaging Abnormalities (ARIA) [4]. Only 17 % of eligible patients in a monocentric American cohort met none of the exclusion criteria for lecanemab treatment [5]. American and Korean guidelines have already been published to support the use of lecanemab in clinical practice adapted to available resources and existing national clinical practices [6,7]. The *Fédération des Centres Mémoire* (French Federation of Memory Clinics - *FCM*) proposes its recommendations in this document to enable clinicians to select patients, administer lecanemab and monitor its possible side effects in the French Healthcare system with an optimal risk-benefit ratio.

The methods of these recommendations are detailed in the Supplementary Material. To accommodate an international audience and stimulate discussions among different healthcare systems around the world, we also provide a summary of key points regarding the current French context for clinical diagnosis and treatment of AD in the Supplementary Material.

## 2. Recommendations for prescription and administration

### 2.1. How should the indication for lecanemab be determined and discussed?

#### 2.1.1. Arguments

The CLARITY-AD trial showed positive results for 10mg/kg lecanemab infusions every two weeks in primary and secondary outcomes, including Caregiver Burden and Quality of Life [8]. However, concerns have been raised about its clinical relevance at 18 months and beyond, due to the modest effect size and uncertainty regarding long-term efficacy [9–11]. Besides, using the EMA side effects frequency classes terminology [12], ARIA were “very common” (21.5 %), serious adverse events due to ARIA “common” (1.1 %), and deaths due to ARIA “uncommon” (at least 1 case was reported in the open-label extension with no obvious confounding factor, 4 in all) [13]. These findings highlight the importance of a careful, individualized, risk-benefit evaluation, including clinical, neuropsychological, biological, genetic, and imaging data, before treatment initiation.

#### 2.1.2. Recommendations

We recommend an open, multidisciplinary consultation meeting to discuss the indications and contraindications of lecanemab. The attendees of this meeting should at least include one physician from a *CMRR* (*Centres Mémoire de Ressources et de Recherche* – Tertiary Memory Clinic) with expertise in anti-amyloid antibodies, such as a geriatrician, a neurologist, or a psychiatrist, along with a neuroradiologist. Ideally, the meeting should also involve a neuropsychologist and a nuclear medicine specialist for a more comprehensive perspective. The meeting will particularly assess the individualized risk of symptomatic and severe ARIAs (see specific section).

Discussions from these meetings should be communicated with appropriate language to the patient and their care partner for a shared-decision making process. While the presence of a care partner is preferable, their absence is not a contraindication for lecanemab treatment.

### 2.2. In which facility should lecanemab be administered?

#### 2.2.1. Arguments

In France, the location of drug administration is determined by regulatory prescribing information. Due to its high cost and adverse events, accessibility to the drug is expected to be limited. Therefore, it is likely that the drug will be restricted to hospital use, especially during the initial commercial stages.

#### 2.2.2. Recommendations

Drug administration should be, first and foremost, aligned with regulatory prescribing information. Ideally, they should not be limited to certified Memory Clinics such as *Consultation Mémoire de Territoire* (Territorial Memory Consultation), or *CMRR*. However, the facility must have essential resources, including participation in the French Alzheimer's registry (*BNA*, *Banque Nationale Alzheimer*), ability to manage infusion reactions, and access to brain MRI (1.5 or 3T) for contraindications assessment and ARIA monitoring. The facility must also have set up a care pathway for monitoring and managing ARIA, and proposed a specific training on ARIA for radiologists. At present, home treatment administration is not approved. Nevertheless, progress in drug delivery systems and safety may open the door for future consideration of home treatment administration feasibility.

## 3. Recommendations for assessing eligibility based on the severity of cognitive and functional impairments

### 3.1. How can the early stage of the disease be assessed in routine clinical practice to determine eligibility for lecanemab?

#### 3.1.1. Arguments

Lecanemab has been tested in patients with early AD in CLARITY-AD, including MCI due to AD and mild AD dementia [14–16]. The patients had cognitive complaints and impairment in one or more cognitive domains but no or mild decline in autonomy, with Mini Mental Status Evaluation (MMSE) score between 22 and 30, and CDR global score of 0.5 for MCI and 0.5 to 1 for mild dementia. *Post-hoc* analyses showed clinical benefits in both MCI and mild AD subgroups [2].

Various clinical criteria can help assess AD severity. Diagnostic and Statistical Manual of Mental Illnesses fifth edition (DSM-V) criteria, for instance, differentiate between minor and major neurocognitive disorders based on interference with independence. The DSM-V suggests three levels of severity for major neurocognitive disorders: mild (instrumental activities of daily living), moderate (basic activities of daily living), and severe (fully dependent) [17].

The MMSE is commonly used to assess the level of cognitive impairment but may overestimate its severity in individuals with lower educational levels, non-native language speakers, or progressive aphasia [18–20]. In such cases, the threshold of 22/30 may require reconsideration.

The Lawton Instrumental Activities of Daily Living (IADL) scale, recognized for its user-friendly design and reliability, is commonly used in clinical and research contexts to describe a patient's ability to manage complex daily tasks [21]. Combining the Lawton scale with other assessment tools, like the CDR scale, can yield a more balanced understanding of the disease's stage and its implications for patient care.

#### 3.1.2. Recommendations

Aligned with the EMA marketing authorization, lecanemab is recommended for patients with early AD, including MCI or mild AD dementia [22,23]. We recommend that this could also be understood as minor and major neurocognitive disorder with a mild impact on daily functioning, according to DSM-V criteria [24].

A MMSE score of 22 or higher is typically required, though lower scores may apply to individuals with limited education or language abilities.

We emphasize the integration of functional assessments into clinical evaluations for a more comprehensive perspective on AD stage beyond cognitive measures such as the MMSE. A CDR global score of 0.5 or 1 is recommended when considering treatment. While we do not propose a specific cutoff score for the Lawton IADL scale to determine treatment eligibility, we recommend its use to support a thorough functional assessment, which is crucial for guiding multidisciplinary team decisions regarding the treatment of complex older adults.

#### 4. Recommendations for assessing eligibility based on clinical phenotype and biomarkers

##### 4.1. Which clinical phenotypes and biomarker profiles qualify for treatment with lecanemab?

###### 4.1.1. Arguments

Lecanemab was tested in patients with memory impairment (Wechsler Memory Scale IV - Logical Memory 2 < 1 SD, WMS IV - LM II), and a positive AD biomarker (visual reading of amyloid PET or CSF total tau/A $\beta$ 42 ratio). Atypical forms of AD were not excluded if they met inclusion criteria.

AD is the primary pathological diagnosis in primary progressive amnesic syndrome (~75–80 % [25]), logopenic variant primary progressive aphasia (~76 % [26]), and posterior cortical atrophy (~94 % [27]). Amyloid PET imaging, fluid biomarkers, and comorbid pathology are comparable between these three phenotypes of AD [28–32]. These findings support the classification of these three phenotypes as common AD phenotypes according to the 2021 International Working Group AD diagnostic criteria [33]. Therefore, there are no obvious biological arguments against the effectiveness of AD pathology-targeting treatments for these patients. Moreover, *APOE4* prevalence, which increases the ARIA risk (see specific section), is usually lower in atypical AD (~40 %) than in CLARITY-AD (69 %) [34,35], suggesting an acceptable risk-benefit profile in atypical AD. However, on top of amyloid pathology and *APOE4* status, these patients may be different in terms of age, sex, prognosis, tau pathology, and psychiatric comorbidities [35,36] that should be carefully reviewed during the risk-benefit ratio assessment in multidisciplinary meetings (see specific sections). Moreover, the CDR and other conventional outcomes may not fully capture the distinct deficits associated with atypical AD phenotypes, which may limit the applicability and relevance of observed treatment effects to their specific condition.

Caution should be emphasized for uncommon phenotypes of AD, i.e., the cortico-basal syndrome, the behavioral variant, the dysexecutive variant, and the non-logopenic variants of primary progressive aphasias [33]. In these situations, Alzheimer's pathology can often be a comorbid and not the primary condition [26,37–40]. As a result, anti-amyloid immunotherapies may have reduced efficacy while retaining side effects, impacting the therapeutic index of these treatments. While criteria have been proposed for behavioral and dysexecutive variants of AD [41,42], they have not been tested across large neuropathological series, preventing the evaluation of their ability to distinguish AD as the primary or a comorbid pathology. Similarly, in individuals with another phenotype outside the common or uncommon phenotypes of AD, biomarker positivity is more likely to prove AD as a comorbid pathology [43]. To date, the clinical efficacy of lecanemab has not been supported by any data for asymptomatic AD biomarker-positive individuals or those with AD pathology as a comorbid condition.

Several CSF biomarkers have been validated for clinical use, but the combined interpretation of two CSF biomarkers can improve diagnostic accuracy. The "A + /T+ approach" and ratios (A $\beta$ 42/40, pTau181/A $\beta$ 42) have both been shown to have higher diagnostic accuracy than individual biomarkers [37,44]. The CSF "A + /T+ approach" demonstrated 100 % specificity but lower sensitivity (65 %), while A $\beta$ 42/40 and pTau181/A $\beta$ 42 ratios had higher sensitivity (86–89 %) and high but not 100 % specificity (92–96 %). The total tau/A $\beta$ 42 ratio used in CLARITY-AD has received less evidence against neuropathological validation. Ad-

ditionally, amyloid PET demonstrates high sensitivity and specificity (sensitivity 96–98 %, specificity 89–100 %) [45,46]. In France, CSF analysis is recommended as the first-line investigation for AD biomarkers, with amyloid PET recommended as a 2nd-line investigation if lumbar puncture is contra-indicated or if CSF analysis results are inconclusive. Tau PET has recently been granted EMA approval but has not yet been approved in France. Its prescribing information and reimbursement remain to be established. We do not anticipate an important role for tau PET in selecting or monitoring patients for lecanemab, as its availability will likely remain limited, as for amyloid PET.

Plasma biomarkers, especially pTau217, have demonstrated excellent diagnostic performances against amyloid PET [47]. They are transitioning to clinical practice, as most widely used automated test equipment manufacturers for CSF AD biomarkers in France have submitted FDA regulatory filings for pTau 217/ $\beta$ -Amyloid 1–42 plasma ratio (Fujirebio® Lumipulse) or have been granted FDA Breakthrough device designation for plasma pTau217 (Roche® Elecsys). Contrary to Tau PET, we anticipate that the availability, limited invasiveness, and cost of plasma biomarkers will facilitate the care pathways imposed by lecanemab. In France, the reimbursement for the measurement of phosphorylated-tau species and A $\beta$  peptides applies to all fluids, not just CSF, thereby already allowing the reimbursement of plasma measurements. Applying a double threshold to classify results into three categories (negative, intermediate, positive) enables the adjustment of sensitivity and specificity to meet specific clinical requirements, such as a very high positive predictive value [48]. Moreover, recommendations for the use of plasma biomarkers have recently been published to facilitate the process of selecting eligible patients for treatment [49].

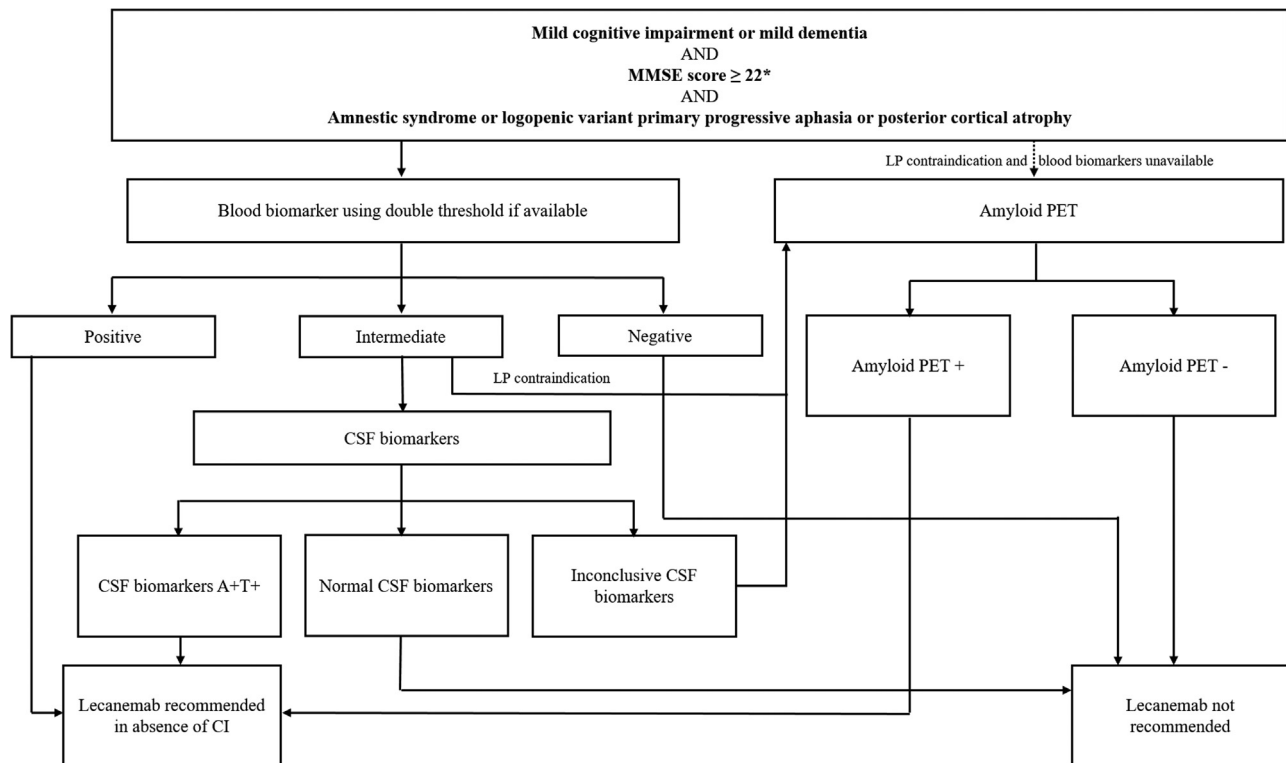
###### 4.1.2. Recommendations

Cognitive testing and AD biomarker investigation are mandatory before starting lecanemab therapy (Fig. 1). Given the complexity of lecanemab treatment, it is essential to prioritize a high positive predictive value of the diagnostic procedure by ensuring both high biomarker specificity and pre-test probability for Alzheimer's pathology.

Lecanemab is recommended for common AD phenotypes (amnesic syndrome [a.k.a. as typical], logopenic variant primary progressive aphasia, or posterior cortical atrophy) with abnormal CSF biomarkers (A+ /T+) or positive (visual reading) amyloid PET. In case of inconclusive CSF analyses (A- /T+ or A+ /T-), we recommend performing amyloid PET to confirm biomarker positivity (in A- /T+ individuals, the A- status should first be confirmed by a normal A $\beta$ 42/40 ratio before considering second-line amyloid PET).

Lecanemab is not recommended for uncommon AD phenotypes (cortico-basal syndrome, dysexecutive variant, behavioral variant, non-logopenic variants of primary progressive aphasia) or any other phenotype, regardless of AD biomarker positivity. Lecanemab is not recommended for asymptomatic AD biomarker-positive individuals.

Plasma biomarkers, once fully approved, may serve for AD biomarker investigation for lecanemab eligibility, reducing the need for invasive lumbar punctures and associated discomfort and sampling costs. To achieve a high positive predictive value in this therapeutic context, we recommend employing a double-threshold approach. The high threshold should differentiate between intermediate and positive results categories with a specificity of at least 97.5 % against CSF or PET gold standards. This ensures a positive predictive value of  $\geq$  99 % when the pre-test probability of Alzheimer's pathology is  $\geq$  70 %, typical of common AD phenotypes. Under these conditions, similar to the current performances of CSF and PET biomarkers, a patient with a common AD phenotype classified as positive based on a plasma biomarker may be considered eligible for lecanemab. Individuals in the intermediate category should continue to undergo lumbar puncture or amyloid PET. For those with negative plasma results, further assessment via lumbar puncture or amyloid PET should be determined on a case-by-case basis, considering the negative predictive value. Careful attention must be given to the threshold set for plasma test positivity, as the recommended



**Fig. 1.** recommendations related to cognitive severity, phenotype and biomarkers profiles.

Abbreviations: CI, contraindication; CSF, CerebroSpinal Fluid; LP, Lumbar Puncture; MMSE, MiniMental State Examination; PET, Positron Emission Tomography. \*To be discussed in multidisciplinary consultation meetings for individuals with low education or language abilities.

double threshold with 97.5 % specificity may differ from the standard thresholds provided by manufacturers or laboratories.

Multidisciplinary meetings may discuss exceptional cases outside these recommendations at the discretion of the attending physician.

## 5. Recommendations for assessing eligibility based on *APOE* genotype

### 5.1. Is the knowledge of the *APOE* genotype status necessary to be eligible for lecanemab?

#### 5.1.1. Arguments

*APOE* genotype served as a randomization stratum in the CLARITY-AD trial, limiting the risk of bias in the subgroup analysis. Post-hoc analyses revealed that lecanemab's efficacy in *APOE4* homozygotes was numerically centered around zero, unlike the clearer benefits observed in heterozygotes and non-carriers (after 18 months of follow-up, the CDR-SB evolution was 1.22 for patients on lecanemab, compared to 1.75 for the placebo group among the 1521 *APOE4* heterozygotes and non-carriers). *APOE4* homozygotes face significantly higher risks of ARIA compared to other genotypes, with ARIA-edema (ARIA-E - 32.6 %) and ARIA-hemorrhage (ARIA-H - 38.3 %) rates markedly elevated under treatment. Preliminary data from the Open-Label Extension showed similar ARIA incidence for a total of 1612 treated patients, including 249 *APOE4* homozygotes [50]. *APOE4* genotype was often reported in severe cases of ARIA [13,51,52], and the two published cases of death with concomitant serious ARIA were *APOE4* homozygotes [13,51]. These findings justified EMA's decision to restrict lecanemab use to patients with one or no *APOE4* copy.

#### 5.1.2. Recommendations

Aligned with the EMA recommendation, we recommend that *APOE* genotyping be performed for all treatment candidates to provide valu-

able information for risk discussions in *APOE4* heterozygotes and assess the risk-benefit ratio for lecanemab. *APOE4* homozygotes should not receive lecanemab, as currently available data shows an unfavorable risk-benefit ratio. It is important to counsel patients on the implications of genetic testing, as it has a crucial role in appropriate treatment discussions and impacts their relatives.

## 6. Recommendations for assessing eligibility based on age and frailty

### 6.1. Is there a lower age limit to receive lecanemab?

#### 6.1.1. Arguments

Symptoms of AD usually develop after 65 years of age, but around 5.5 % of cases begin before 65, known as early-onset AD (EOAD) [53]. Late-onset AD (LOAD) and EOAD share similar core neuropathological features [54]. The role of  $\beta$ -amyloidosis in both EOAD and LOAD pathogenesis is well-established [55], providing a rationale for evaluating anti-amyloid immunotherapies in EOAD patients with autosomal dominant mutations [56].

However, EOAD differs from LOAD regarding clinical, genetic, and pathophysiological features that may affect clinical trials outcomes. EOAD patients exhibit more frequently an accelerated disease course [57], atypical clinical phenotypes [58], higher grey matter atrophy, different topographical distribution of tau pathology on tau-PET [58–61], higher density of neurofibrillary tangles [32] and a less frequent but highly prevalent non-AD copathology [32]. They also have a higher likelihood of carrying two *APOE4* alleles [62] or autosomal dominant pathogenic variants in the *APP*, *PSEN1*, or *PSEN2* genes, which may also confer a higher risk of cerebral amyloid angiopathy (CAA).

The CLARITY-AD study did not include individuals under 50, and other trials using anti-amyloid immunotherapies have set the minimum age for inclusion between 50 and 60. Therefore, limited data is avail-

able on younger patients, except for those included in the Dominantly Inherited Alzheimer Network Trial Unit that tested other anti-amyloid immunotherapies than lecanemab [56]. This population does not appear to have a higher incidence of ARIA [63].

Post-hoc analyses of EOAD patients from CLARITY-AD (353 patients aged between 50 and 65 years old) did not show a significant benefit of lecanemab over placebo on CDR-SB and ADAS-Cog14. However, because age was not a randomization stratum, the validity of these post-hoc analyses is limited. Safety data for subjects under 65 were not specifically reported.

### 6.1.2. Recommendations

We recommend against setting a lower age limit for anti-amyloid immunotherapy. Our position is that chronological age alone is not the determining factor that affects the risk-benefit ratio, but rather the pathological and genetic traits associated with EOAD (which can be exclusion criteria, like *APOE4* homozygosity). We do not recommend excluding EOAD individuals with autosomal dominant inherited mutation unless they exhibit imaging features of CAA (see specific section). However, a comprehensive risk assessment is still necessary, especially considering their genetic background, which may increase the risk of ARIA. Since efficacy data is currently limited, detailed and clear information about uncertainty should be provided to the patient and their care partner.

## 6.2. Is there an upper age limit to receive lecanemab?

### 6.2.1. Arguments

The CLARITY-AD protocol excluded subjects over 90, while 239 participants (13.3 %) were over 80 years old. The clinical effect size in the CLARITY-AD participants over 75 was numerically favorable in a post-hoc analysis, similar to that reported by the aducanumab phase III EMERGE clinical trial [64]. In contrast, the donanemab phase III clinical trial showed no noticeable age effect [65].

Lecanemab administration was limited to patients below 90 in CLARITY-AD to avoid high screen failure and attrition rates in elderly subjects [66]. Multimorbidity or polypharmacy in the oldest adults may hinder their access to lecanemab therapy (see specific section). Non-neurological disorders, such as malnutrition, significantly influence the course of cognitive decline in older adults [67]. Anticholinergic drugs, hearing loss, or sarcopenia have also been pointed out as predictors of faster evolution [68–70]. Although the effect of lecanemab has not been studied in AD patients with such comorbidities, they should be considered in the risk-benefit ratio assessment.

### 6.2.2. Recommendations

We do not recommend chronological age-based restriction for lecanemab therapy. Rather than age, comorbidities and functional status affecting the risk-benefit ratio should be considered. As lecanemab treatment requires multiple visits, attention should be paid to mobility disorders, chronic pain, or mental health conditions that may affect the oldest patients' quality of life.

When deemed necessary, the oldest candidates should be referred to a geriatrician for a comprehensive geriatric assessment, which can inform multidisciplinary consultation meetings.

## 6.3. Should frailty be assessed in older adults before considering lecanemab therapy?

### 6.3.1. Arguments

Frailty, a condition that increases susceptibility to stressors and reduces physiological reserves, predicts chemotherapy intolerance and poor treatment outcomes in older adults with cancer [71,72]. Frailty is linked to the odds of AD dementia, and as it increases, the relationship between pathology and dementia weakens [73]. Although no data is currently available regarding the effect of lecanemab in frail patients, frailty may influence the efficacy of anti-amyloid immunotherapy.

### 6.3.2. Recommendations

Frailty scales like the FRAIL scale [74] or Fried's criteria [75] could be used as screening tools to refer the oldest AD patients for a comprehensive geriatric assessment before introducing anti-amyloid immunotherapies. These tools can help identify the need for a comprehensive evaluation of geriatric syndromes and facilitate a multidisciplinary discussion. However, the relevance of frailty scales in this context requires further investigation.

## 7. Recommendations for assessing eligibility based on comorbidities and concomitant medications

### 7.1. Which comorbidities limit eligibility for lecanemab?

#### 7.1.1. Arguments

Over 50 % of CLARITY-AD participants received symptomatic AD treatments (acetylcholinesterase inhibitors, memantine), which served as a randomization stratum. Post-hoc analyses did not reveal any significant difference in lecanemab efficacy between individuals taking or not taking these drugs.

Lecanemab was not tested in the presence of any other neurological conditions, metabolic dysfunction, infectious disease, sensory loss, substance abuse, or psychiatric disorders that could interfere with study procedures or indicate a dementia diagnosis other than AD. Comorbid conditions that could affect drug efficacy and/or safety (e.g., other immunotherapies or immunosuppressors, any uncontrolled immunological disease), or significantly impact the prognosis of the participant (e.g., malignant neoplasms, cardiac, respiratory, gastrointestinal, renal disease which are not stably and adequately controlled) were excluded.

Females who were breastfeeding or pregnant were excluded from the CLARITY-AD trial.

#### 7.1.2. Recommendations

Acetylcholinesterase inhibitors and memantine can be continued or initiated during the lecanemab treatment period.

Given the lack of data on the interaction of lecanemab with numerous comorbid conditions, multidisciplinary meetings should review comorbid conditions and address the following questions to assess the risk-benefit ratio:

- 1) Does the comorbid condition primarily and significantly affect cognition and function despite positive biomarkers?
- 2) Will the comorbid condition likely interfere with the expected safety, magnitude, and temporality of lecanemab's efficacy, thereby impacting its risk-benefit ratio?
- 3) Will the comorbid condition likely affect treatment compliance and monitoring?

Behavioral and psychological symptoms of comorbid primary psychiatric disorders must be distinguished from those due to AD.

## 8. Recommendations for MRI assessments

### 8.1. What are the best MRI sequences for the detection of ARIA-H?

#### 8.1.1. Arguments

ARIA-H refers to hemosiderin deposits detected on T2\*-weighted gradient echo (GRE-T2\*) or susceptibility-weighted imaging (SWI) MR sequences. The STAndards for Reporting Vascular changes on nEuroimaging (STRIVE) criteria recommend GRE-T2\* or SWI [76] sequences, with GRE-T2\* as the only option used in anti-amyloid immunotherapy trials [4]. The image acquisition protocol in France depends on the local center, based on either GRE-T2\* or SWI on a 1.5 or 3 Tesla scanner.

SWI sequences, with higher magnetic field and thinner slice thickness, provide better lesion contrast for CMH, enabling the detection of smaller and around three times more CMH than GRE-T2\* [77]. SWI ratings also demonstrate greater disseminated cSS and higher multifocality

scores [78]. Due to the increased sensitivity of SWI sequences, more patients would be excluded from treatment with lecanemab when using similar CMH cutoffs, as its imaging protocol was based on the GRE-T2\* sequence.

Most clinical routine GRE-T2\* sequences differ from those employed in CLARITY-AD and anti-amyloid clinical trials. These trials have established CMH and cSS cutoffs using longer echo times (TE) ( $\geq 20$  ms) [4], impacting microhemorrhage detection [79].

### 8.1.2. Recommendations

We recommend using GRE-T2\* sequence with long TE ( $\geq 20$  ms) to detect ARIA-H since there is no established equivalence between CMH cutoffs determined with long TE GRE-T2\* and SWI sequences. If baseline imaging has been performed with a SWI sequence, we recommend performing MRI monitoring with the same sequence and field strength (1.5 or 3T).

Real-world registries will help establish equivalence between SWI and GRE-T2\* sequences with long TE to determine the CMH, cSS thresholds for lecanemab eligibility and monitoring.

## 8.2. What are the MRI-based contraindications?

### 8.2.1. Arguments

In CLARITY-AD, MRI was required for eligibility and safety monitoring. MRI-based exclusion criteria during screening included evidence of other clinically significant lesions indicating a dementia diagnosis other than AD, cerebral contusion, encephalomalacia, unruptured intracranial vascular malformations, infectious lesions, multiple lacunar infarcts or stroke, severe small vessel disease, space-occupying lesions, or brain tumor. Exclusion criteria for MRI scans were implemented to identify MRI risk factors of ARIA, including severe ARIA-E, and hemorrhage:  $\geq 5$  cerebral microhemorrhages (CMH,  $\leq 10$  mm in the greater diameter),  $\geq 1$  macrohemorrhage ( $>10$  mm),  $\geq 1$  area of focal or disseminated cortical superficial siderosis (cSS), evidence of vasogenic edema.

MRI risk factors of ARIA include pre-existing lobar CMH and cSS, highlighting CAA as an important risk factor for ARIA [6,80,81]. The Alzheimer's Association research roundtable workgroup recommended a cutoff value of 4 for the number of CMH (without explicitly stating their lobar location) [7]. However, this cutoff may not fully estimate the global hemorrhagic risk due to CAA. Baseline CMH are known to increase ARIA risk, identified even in cases with less than four CMH [82]. In gantenerumab and donanemab trials, where patients with one cSS were eligible, cSS was associated with a higher risk for ARIA [81,82]. A recent death from a cerebral macrohemorrhage on trontinemab was also reported in a phase Ib/IIa study in a patient with baseline cSS [83]. In patients with CAA, cSS is a risk factor for future first-ever symptomatic intracerebral hemorrhage (ICH) [84]. Boston Criteria v1.5 for probable CAA are the best predictors of ICH risk in clinically-diagnosed CAA patients [85,86], particularly the presence of cortical or cortical-subcortical hemorrhage and/or cSS, contrary to Boston v2.0 criteria [86]. Conversely, deep hemorrhages, commonly associated with hypertension, are not indicative of CAA. Cardiovascular risk factors for arteriosclerosis do not generally increase the ARIA risk [81,87]. However, high mean arterial pressure ( $\geq 107$  mmHg) and antihypertensive treatments were found to be associated with an increased and lesser risk, respectively, of ARIA-E in the phase 3 clinical trial of donanemab [82].

Neuropathologically-defined CAA is frequently associated with AD (79.2 % of AD cases exhibit any form of CAA, while 23.3 % display severe CAA) [88], but the incidence of ARIA was found to be much lower in the CLARITY-AD study (12.6 % of ARIA-E and 17.3 % of ARIA-H). This suggests that any form of comorbid CAA is not the only factor underlying ARIA.

### 8.2.2. Recommendations

Patients with MRI contra-indications should avoid lecanemab therapy as MRI is necessary for risk-benefit evaluation and safety monitor-

ing. Specific cases of MRI-compatible pacemakers should be discussed on a case-by-case basis, notably considering the potential need for unplanned MRI in the case of ARIA.

A recent baseline brain MR ( $<6$  months), is recommended before administering lecanemab. New or unusual neurological symptoms within these 6 months should prompt a new MRI.

Patients with at least one of the following MRI risk factors for ARIA and/or ICH should be excluded from lecanemab therapy:

- $\geq$  Two lobar CMH (Boston v1.5 criteria for probable CAA) [85],
- $\geq$  Five CMH (anywhere in the brain),
- $\geq$  One area of cSS (focal or disseminated),
- $\geq$  One macrohemorrhage  $>10$  mm,
- Recent evidence of vasogenic edema,
- Multiple lacunar infarcts,
- Severe subcortical white matter hyperintensities (Fazekas 3),
- Ischemic stroke involving a major vascular territory must be evaluated on a case-by-case basis, considering the patient's age, the cause, the hemorrhagic risk, and the potential link of the affected territory with cognitive decline.

Additionally, patients with brain lesions deemed to primarily cause cognitive decline should also be excluded from lecanemab therapy, as in CLARITY-AD.

Collecting baseline and follow-up MRI markers based on Boston criteria v1.5 and v2.0 features will be essential to comprehend the relationship between CAA and ARIA [85,89].

## 9. Recommendation for MRI follow-up

### 9.1. What should the MRI monitoring be during treatment?

#### 9.1.1. Arguments

In CLARITY-AD, safety MRIs were performed before the 5th, 7th, 14th, 27th, and 40th biweekly infusions of lecanemab and at each clinical suspicion of ARIA. The EMA and the FDA recommend obtaining an MRI before the 5th, 7th, and 14th infusions, regardless of the APOE status, and whenever ARIA is suspected. The US Appropriate Use Recommendations (AUR) recommend an additional MRI before the 26th infusion for APOE4 carriers and those with a history of ARIA.

Around 50 % of ARIA cases occurred before week 8 (before 5th infusion) for APOE4 homozygotes, week 11 (before 7th infusion) for APOE4 heterozygotes, and week 6 (before 4th infusion) for non-APOE4 carriers patients [50]. 80 % of ARIA cases occurred before week 24 (before 13th infusion) for APOE4 homozygotes, week 25 (before 14th infusion) for APOE4 heterozygotes, and week 11 (before 7th infusion) for non-APOE4 carriers [50]. ARIA was still observed in approximately 1 % of non-APOE4 patients after week 11 (7th infusion), and in approximately 4 % of patients, only APOE4 carriers, after week 26 (14th infusion) [50]. After week 53 (27th infusion), ARIA was still observed in approximately 1 % of patients, only APOE4 carriers [50].

The two published deaths with concomitant serious ARIA were APOE4 homozygotes who experienced severe ARIA symptoms after the 3rd infusion of lecanemab [13,51].

#### 9.1.2. Recommendations

In line with the EMA recommendation, we recommend safety MRI scans before the 5th, 7th and 14th infusions and whenever ARIA is suspected, regardless of the APOE status.

Given the observed ARIA rate in the CLARITY-AD trial, we also recommend an additional MRI before the 3rd infusion. For APOE4 carriers, an MRI before the 27th infusion is recommended due to the residual ARIA risk in this group (Fig. 2 and Table 1).

The ARIA risk declines to approximately 1 % in non-APOE4 carriers earlier than in APOE4 carriers. If confirmed in real-world clinical practice, the MRI monitoring before the 14th infusion in non-carriers may be deemed unnecessary in the future.

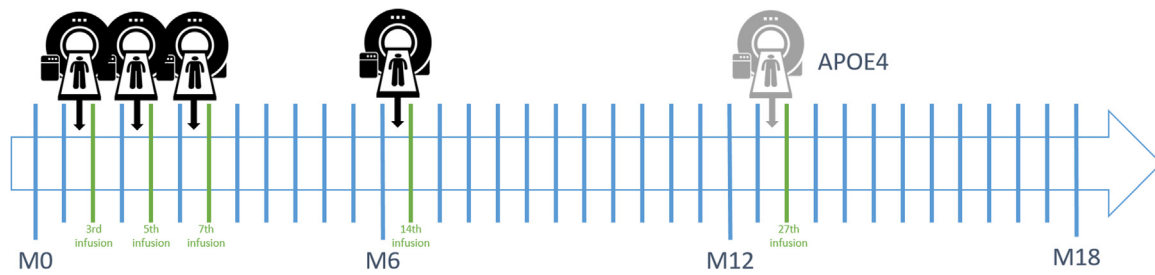


Fig. 2. MRI monitoring to screen for ARIA.

Blue vertical bars illustrate biweekly lecanemab infusions. Green vertical bars illustrate lecanemab infusions requiring a safety MRI before infusion initiation. Grey MRI icons illustrate additional MRI monitoring in *APOE4* carriers only.

**Table 1**  
MRI monitoring to screen for ARIA.

MRI scan		CLARITY-AD criteria	American recommendations [6]	French recommendations
<b>Monitoring</b>	<i>APOE4</i> carriers	Week 9, week 13, month 6, month 12 and month 18	Before the 5th, 7th and 14th infusions Additional safety MRI before the 26th infusion	Before the 3rd, 5th, 7th and 14th Additional safety MRI before the 27th infusion
	<i>APOE4</i> -non carriers	Week 9, week 13, month 6, month 12 and month 18	Before the 5th, 7th and 14th infusions	Before the 3rd, 5th, 7th and 14th infusions
<b>Sequences</b>	ARIA-H detection	GRE-T2*	GRE-T2* or SWI	Preferably GRE-T2* sequence with long TE (same sequence for ARIA monitoring)
	ARIA-E detection	FLAIR and DWI	FLAIR and DWI	FLAIR and DWI
<b>Magnet</b>		1.5T or 3T magnet	Preferably on a 3T magnet	1.5T or 3T magnet (Same MRI machine for monitoring)

## 10. Recommendations for assessing eligibility based on the use of antithrombotic agents

### 10.1. What are the recommendations related to anticoagulants and antiplatelets use?

#### 10.1.1. Arguments

The EMA has recommended that lecanemab must not be used by people receiving anticoagulant treatment. Only 79 participants received anticoagulants in CLARITY-AD. The overall ICH incidence was 0.6 % (5/898) in the active group [2,50]. However, the incidence increased approximately fivefold in subjects on anticoagulants (2.5 %, 2/79) compared to those without antiplatelets or anticoagulants (0.6 %, 3/545). There was no anticoagulant effect on the incidence of CMH and cSS.

Antiplatelet agents did not appear to increase the risk of ICH, and the effect of dual antiplatelet therapy was not assessed.

Preliminary data from the Open Label Extension show similar hemorrhage rates for a total of 1612 treated patients, including 147 on anticoagulants, and 8 ICH (2.7 % in patients on anticoagulants, 0.4 % in those without antiplatelets or anticoagulants) [50].

The cognitive efficacy of lecanemab was not significant in the subgroup of participants on anticoagulants in a post-hoc analysis.

The aducanumab and gantenerumab phase 3 clinical trials excluded patients on anticoagulants [64,90]. The safety results from the donanemab phase 3 trial did not differentiate between types of hemorrhage [65].

#### 10.1.2. Recommendations

Aligned with the EMA, we recommend against lecanemab for patients on anticoagulants due to an unfavorable risk-benefit ratio.

If a patient on lecanemab requires anticoagulation, temporary or definitive discontinuation of lecanemab may be necessary, depending on the indication of anticoagulants:

- For temporary anticoagulation (e.g., pulmonary embolism or deep-vein thrombosis of the lower limbs without persistent risk factors), temporary discontinuation of lecanemab is recommended.
- For long-term anticoagulation (e.g., atrial fibrillation (AF)), permanent discontinuation of lecanemab is recommended. Performing sys-

tematic percutaneous left atrial appendage occlusion is not recommended as a routine procedure for patients with AF on lecanemab to avoid anticoagulation [91]. An individualized decision may be considered in a multidisciplinary meeting based on the risk-benefit ratio of the procedure and lecanemab continuation.

As per CLARITY-AD protocol and American AUR, patients with an uncontrolled bleeding disorder (platelet count <50,000 or international normalized ratio [INR] >1.5 for non-anticoagulant participants) should not receive lecanemab [2,6].

While antiplatelet agents can be used with lecanemab treatment, caution is advised with dual antiplatelet therapy due to the increased risk of bleeding and lack of data.

These recommendations may lead to an update in the future. For instance, current data indicate the highest risk of ARIA-E and -H within the initial 1–6 months following the initiation of lecanemab (see specific section). If an anticoagulant needs to be initiated on lecanemab, based on the treatment duration and recency of MRI monitoring and ARIA symptoms, it might be reasonable to differentiate between low (>6 months on lecanemab, no recent radiological ARIA, no current ARIA symptom) and high-risk (<6 months on lecanemab, or recent radiological ARIA, or current ARIA symptom) situations in the future.

Caution is recommended when initiating anticoagulant therapy in non-neurological emergencies for patients receiving lecanemab. A multidisciplinary discussion involving the on-call neurologist is ideal before therapy initiation. However, in urgent, severe, and life-threatening cases, the need for anticoagulants must prevail.

### 10.2. What are the recommendations related to the use of intravenous thrombolytics?

#### 10.2.1. Arguments

One case report has been published describing fatal cerebral hemorrhages in a 65-year-old *APOE4* homozygote on lecanemab (3 infusions) who received alteplase for suspicion of ischemic stroke [51]. Emergency CT revealed early (~2 h after symptoms onset) hypodensities in multiple vascular territories and occlusion of the M3 branch of the left middle cerebral artery (<https://www.fda.gov/media/169263/download>).

The autopsy showed extensive multifocal intraparenchymal hemorrhages, CAA, high AD neuropathologic changes, and diffuse histiocytic vasculitis. Brain MRI that had been performed 81 days before the stroke, as per CLARITY-AD protocol, showed mild small-vessel disease, with no microhemorrhage, edema, or ARIA. In the TRAILBLAZER-ALZ6 trial, one participant from the modified titration group experienced persistent ARIA-E and stroke-like symptoms. Emergency response included the administration of tissue type plasminogen activator therapy; however, the participant died after brain hemorrhage (<https://investor.lilly.com/news-releases/news-release-details/modified-titration-donanemab-demonstrated-reduction-aria-e-early>). Other authors reported that severe ARIA can present as stroke mimics, especially as partial seizures [13,52,92].

In France, most stroke centers have access to a 24/7 rapid MRI in case of acute stroke suspicion.

### 10.2.2. Recommendations

Thrombolytic agents should be considered with extreme caution in patients on lecanemab due to the potential benefit of fibrinolysis in the acute phase of ischemic stroke and the increased hemorrhage risk related to ARIA. Emergency rapid brain MRI should be performed whenever possible to rule out ongoing ARIA [87] and determine the risk-benefit ratio of thrombolytics in this emergency situation. If ARIA is detected or emergency rapid brain MRI is unavailable, alternative treatments such as endovascular therapy should be considered when indicated.

Stroke and emergency clinicians assessing suspected stroke patients should be aware of ARIA as a potential differential diagnosis of stroke, considering the “common” rate of symptomatic ARIA in patients on lecanemab [2,12].

Caution is recommended when initiating thrombolytics in non-neurological emergencies for patients receiving lecanemab. A multidisciplinary discussion involving the on-call neurologist is ideal before therapy initiation. However, in urgent, severe, and life-threatening cases, the need for thrombolytics must prevail.

## 11. Recommendations on ARIA management

### 11.1. What are the recommendations related to the ARIA management?

#### 11.1.1. Arguments

ARIA are usually asymptomatic and resolve spontaneously or after treatment discontinuation [93]. However, when symptomatic, they can cause mild to severe symptoms such as headache, blurry vision, confusion, coma, seizure, or focal neurological deficit [13,52,92,93]. In CLARITY-AD, symptomatic ARIA-E occurred in 2.8 % (25/898) and symptomatic ARIA-H in 1.2 % (11/898), with ICH reported in 5 patients (0.6 %) [50].

A recent case report has highlighted an ischemic stroke associated with ARIA in a patient treated with lecanemab, highlighting similarities with amyloid beta-related angiitis (ABRA) and central nervous system vasculitides [94–96].

An ARIA radiological severity score and the clinical status are used to determine whether lecanemab should be discontinued [93]. Radiologists' training is crucial to comply with recommendations for a standardized imaging protocol and an ARIA reporting template that includes the ARIA severity grading (Table 2) [97].

ARIA's radiological evolution, whether edematous or hemorrhagic, remains poorly understood. A link between ARIA and long-term ventricular enlargement has been suggested [98]. Limited data exist on factors predicting ARIA-E evolution, including its size, expansion rate, decrease, association with ARIA-H, long-term clinical prognosis, recurrence risk, and association with clinical symptoms. Such information would allow for more precise future recommendations on ARIA management.

Corticosteroids have been used to manage symptomatic cases of ARIA based on shared clinical and radiological manifestations of CAA-

related inflammation [92,99]. Early treatment with immunosuppressive drugs such as corticosteroids, cyclophosphamide, or mycophenolate can improve the radiological and clinical course and reduce the likelihood of recurrence in cases of CAA-related inflammation patients [100]. High-dose IV corticosteroids should be slowly oral tapered off to reduce the recurrence of CAA-related inflammation [101]. Plasmapheresis has been considered to reduce the rate of circulating monoclonal antibodies responsible for severe ARIA [102]. In refractory severe cases of small vessels granulomatous vasculitides of the central nervous system, outside CAA-related inflammation, treatments beyond corticosteroids and cyclophosphamide have included discussions on the use of anti-CD20 and anti-IL-6 therapies [103].

### 11.1.2. Recommendations

ARIA management requires adopting prevention, detection, and treatment approaches. Prevention involves assessing and communicating ARIA risk factors in multidisciplinary consultations and shared decision-making processes (see specific section). For detection, radiologists should be trained to use a standardized imaging protocol and ARIA reporting template (see specific section). Optimal treatment involves a clearly defined clinical care pathway with established protocols at each infusion center. Patients and their relatives should receive written documents, such as a smartphone or wallet-sized drug card, outlining ARIA symptoms, contacts, and emergency measures.

ARIA management depends on the severity of radiological abnormalities and clinical symptoms (Fig. 3, Table 2).

- In asymptomatic radiologically mild ARIA, treatment should continue.
- In cases of radiologically moderate or severe ARIA or clinically non-severe symptomatic ARIA, lecanemab infusions should be discontinued. Clinical and MRI follow-up should be based on the severity of symptoms and MRI abnormalities, with careful clinical monitoring, symptom management, and monthly non-contrast MRI until ARIA-E resolves or ARIA-H stabilizes. In cases of radiologically severe ARIA, closer and more frequent scans may be necessary to monitor the progression of edematous lesions.
- In cases of a radiologically severe ARIA-E with mass effect, and the case of clinically severe ARIA-E, high-dose glucocorticoid treatment should be considered (IV methylprednisolone 1g/day for 3–5 days, followed by an oral steroid taper over 3–6 months). Immunosuppressant therapy and plasmapheresis should be considered in the absence of rapid improvement. Anti-epileptic treatment should be started if seizures occur.

Additional factors that may impact management include *APOE4* status, time to last dosing, time course of ARIA, and recurrence of ARIA. In the absence of sufficient data, clinical judgment should guide decision-making.

In case of concomitant ischemic stroke, a standard stroke cause assessment should be performed. If negative, the imputability of ARIA, as an ABRA-like phenomenon, should be discussed in the shared decision-making of long-term antithrombotic treatment.

Lecanemab treatment should not be resumed until ARIA-E has resolved or ARIA-H has stabilized, and this should be communicated for a shared decision-making process. Lecanemab should be discontinued permanently in case of severe symptomatic ARIA, radiological severe ARIA, macrohemorrhage, one area of cSS, or more than two episodes of ARIA.

## 12. Recommendation for treatment duration

### 12.1. When should lecanemab be discontinued?

#### 12.1.1. Arguments

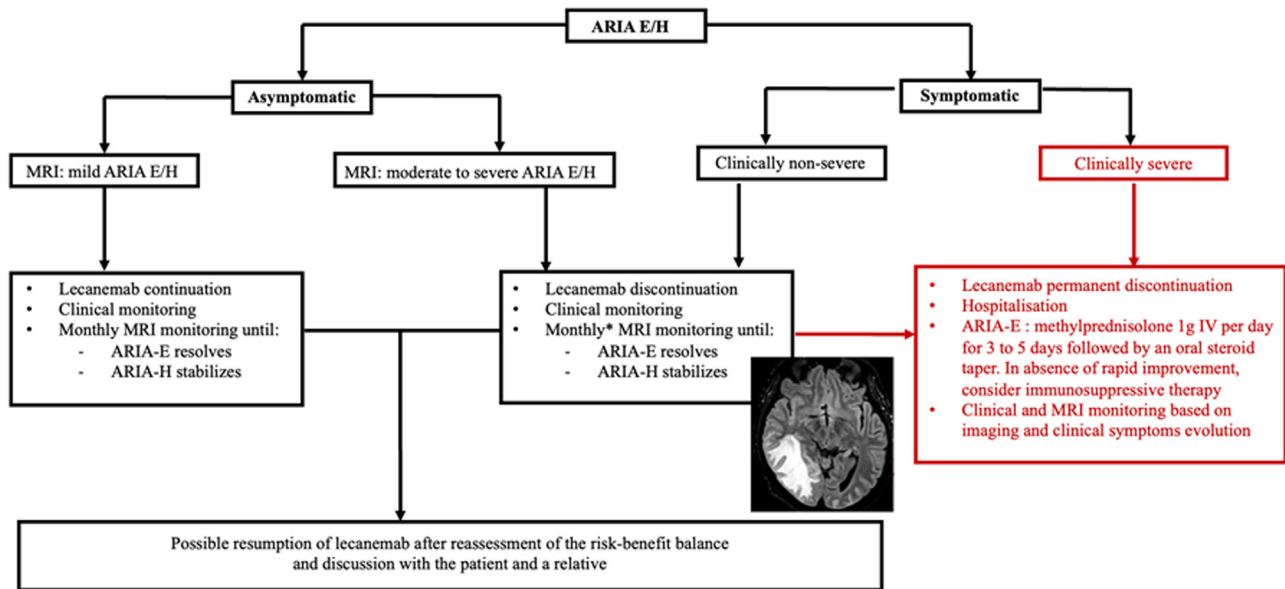
The CLARITY-AD trial continuously treated participants for 18 months at an early stage of AD, without planned drug discontinuation

**Table 2**

ARIA radiographic severity grading inspired by the US FDA Prescribing Information. Note that the severity rating of the cortical superficial siderosis and macrohemorrhage has been adjusted to align with French recommendations.

Type	Mild	Moderate	Severe
<b>ARIA-E</b>	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted.
<b>ARIA-H</b> ARIA-H micro or macrohemorrhage ARIA-H superficial siderosis	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages ≥ 1 macrohemorrhage ≥ 1 area of superficial siderosis

Abbreviations: ARIA-E, Amyloid-related imaging abnormalities-Edema; ARIA-H, Amyloid-related imaging abnormalities-Hemorrhage; FLAIR, FLuid-Attenuated Inversion recovery.



**Fig. 3.** recommendations related to ARIA management.

\* MRI monitoring may be closer, adjusted according to clinical and MRI abnormalities evolution.

Abbreviations: ARIA, Amyloid-related imaging abnormalities; ARIA-H, Amyloid-related imaging abnormalities-Hemorrhage; ARIA-E, Amyloid-related imaging abnormalities-Edema; MRI, Magnetic Resonance Imaging; IV, IntraVenous.

except for safety reasons and participant preference (see specific section). Consequently, both the effect of drug discontinuation and the relevance of lecanemab therapy at later stage of AD are currently unknown. On the other hand, ARIA risk is known to be almost null after 18 months on treatment.

FDA approved a monthly maintenance dosing of lecanemab in patients who completed the 18 months biweekly IV initiation phase [104]. In November 2024, Eisai has completed the rolling submission of a biologics license application to the FDA for lecanemab subcutaneous autoinjector for weekly maintenance dosing.

The donanemab trials took a different approach by testing an anti-amyloid immunotherapy that targets the pyroglutamate form of Aβ. Individuals with negative follow-up amyloid PET were switched to placebo as per the trial protocol. Conversely, lecanemab targets soluble protofibrillar forms of β-amyloid, which are not visible on amyloid PET scans and may have their own toxicity [105].

The long-term effects and disease-modifying properties of lecanemab remain unknown [9]. However, it is worth considering limited case reports of AD patients immunized against amyloid-β (AN1792) and plaque-free for 14 years, who eventually progressed to severe dementia and extensive stages of tau pathology [106].

The general consensus in the field acknowledges that anti-amyloid immunotherapies may not be efficient at later stages of AD [107] and current clinical practice in the US recommends stopping lecanemab infu-

sions once the moderate stages of AD have been reached [108]. Furthermore, the treatment burden should not be underestimated, especially as incapacitation worsens.

**12.1.2. Recommendations**

It is currently impossible to establish an evidence-based guideline for discontinuing lecanemab, except for safety or treatment burden reasons (see specific section). Although a negative amyloid PET might be considered for discontinuing the drug as per the donanemab trials, it is important to note the pharmacodynamic differences between lecanemab and donanemab. We propose here a simple expert consensus statement for lecanemab discontinuation. Therefore, the following good practice statement needs to be updated pending evidence-based practice in the future.

After 18 months of dosing, we suggest systematic, detailed cognitive testing, including the CDR scale. If the patient has progressed to moderate stages of dementia (e.g., CDR global score = 2 or 3, or any equivalent evaluation), we suggest treatment discontinuation. If the patient is still at an MCI or mild dementia stage of AD (e.g., CDR global score = 0.5 or 1, or any equivalent evaluation), we suggest monthly 10mg/kg IV perfusion (or weekly subcutaneous maintenance dosing of lecanemab according to future EMA approval). For these individuals on maintenance dosing, annual detailed cognitive testing could be performed to re-evaluate the dementia stage.

We anticipate reluctance to stop treatment in the moderate stages of the disease, particularly in the absence of alternative therapies. To limit these difficulties, clear, fair, and appropriate information about the conditions for stopping treatment should be part of the shared decision making when lecanemab is initiated.

Any decision regarding drug discontinuation should be discussed in multidisciplinary consultation meetings, considering the changes in the risk-benefit ratio over time and the lack of data.

### 13. Recommendations for the management of infusion-related reactions

#### 13.1. How to manage the infusion-related reactions?

##### 13.1.1. Arguments

In CLARITY-AD, infusion-related reactions occurred in 26.4 % of participants on lecanemab (vs. 7.4 % on placebo) and were the most common symptomatic adverse events. Most reactions were mild to moderate in severity (96 % grade 1 or 2) and usually occurred with the first infusion (75 %) [2].

First-generation antihistamines are often poorly tolerated in the context of cognitive impairment due to their anticholinergic activity [109]. Second-generation antihistamines have a better tolerance profile.

##### 13.1.2. Recommendations

Lecanemab is a humanized antibody and, as per the CLARITY-AD protocol, systematic premedication is not recommended. While severe reactions are rare, emergency medications for anaphylaxis, such as steroids, bronchodilators, oxygen, and epinephrine, must be available at infusion centers. Emergency care pathways and procedures should be established at each infusion center to prepare for possible severe anaphylaxis.

- Grade 1 infusion reactions (mild and transient symptoms such as headache, nausea, abdominal discomfort, elevated blood pressure, chills, ...) require no medication intervention. Infusion may continue.
- Grade 2 infusion reactions (symptoms are moderate to severe and/or persistent, also including rash, fever, and/or vomiting) require immediate discontinuation of the infusion and treatment with 1g of intravenous acetaminophen, 1.5mg/kg of intravenous methylprednisolone and 10 mg of oral cetirizine (or intravenous cetirizine, if available) [110]. The prompt response to these medications defines grade 2 infusion reaction. Infusions of lecanemab may be resumed on subsequent occasions, using the same protocol as a premedication 1 hour before the infusion, with the infusion rate reduced by half.
- Grade 3 (prolonged or recurrent symptoms and/or hospitalization) or grade 4 reactions (life-threatening consequences) require permanent discontinuation of lecanemab and treatment according to local recommendations in agreement with intensive care units.

### 14. Discussion

After EMA approval, lecanemab could be granted Early Market Authorization in France and be used in clinical practice in 2025 [3]. However, transitioning from clinical trials to real-world clinical practice can result in higher adverse events and lower efficacy [111]. To ensure optimal patient outcomes in managing AD, French clinicians should follow standardized approaches to patient selection and administration of lecanemab. These recommendations are aligned with the EMA marketing authorization, i.e. restricted prescription to non-carriers or heterozygous carriers of the  $\epsilon 4$  variant of the *APOE* gene, and to individuals not taking anticoagulants. They do not replace regulatory prescribing information but offer practical information for healthcare professionals in charge of early AD patients.

These recommendations primarily emphasize the need for a comprehensive risk-benefit ratio assessment involving clinical, neuropsychological, biological, genetic, and imaging information that should be discussed in multidisciplinary consultation meetings and communicated to the patient and their care partner using appropriate language to facilitate shared decision-making.

The recommendations for lecanemab are mainly based on its pivotal trial, similar to the American AUR and FDA prescribing information. However, some recommendations differ, (Table 3). We recommend that non-amnesic common AD phenotypes, such as logopenic variant primary progressive aphasia and posterior cortical atrophy, should not be excluded if AD biomarkers are positive. This is based on assessing AD as the likely primary pathology responsible for the patient's phenotype [33]. Conversely, the CLARITY-AD protocol focuses on the amnesic variant, while the US AUR and prescribing information recommend additional information to non-amnesic patients. We recommend refraining from treating *APOE4* homozygotes due to an unfavorable risk-benefit ratio, aligned with the EMA marketing authorization. Conversely, the US AUR and prescribing information advise a careful shared decision-making process. We recommend not treating patients on anticoagulants or with comorbid cerebrovascular disease due to an unfavorable risk-benefit ratio, aligned with the EMA marketing authorization. This aligns with the US AUR but contradicts the FDA's prescribing information, which advises caution. We recommend extending cerebrovascular disease exclusion criteria to individuals fulfilling the Boston v1.5 criteria for probable CAA due to the risk of amyloid-related ICH. Instead of contra-indicating thrombolytics for stroke like the US AUR, we recommend assessing the hemorrhagic risk with a rapid brain MRI when facing emergencies requiring thrombolytic agents or anticoagulants [112,113]. Due to the increased predictive value of cSS for amyloid-related ICH, we recommend discontinuing lecanemab treatment upon any occurrence of cSS until further evidence emerges. This differs from the US AUR guidelines, which allow no baseline cSS and require more than one cSS for permanent discontinuation.

We recommend an additional early safety MRI before the 3rd infusion, considering the early occurrence of ARIA in the CLARITY-AD trial, and to further customize MRI monitoring according to the *APOE4* status. Careful selection of the MRI sequence for detecting hemorrhagic abnormalities is necessary, preferably using long TE GRE-T2\* sequences as long as equivalence between SWI and long TE GRE-T2\* sequences has not been established. It is recommended to establish a clinical care pathway with protocols for patients with ARIA, with trained physicians and radiologists with expertise in neurological emergency and intensive care. Patients on lecanemab should receive emergency cards.

We propose an original approach to integrating AD plasma biomarkers for determining eligibility for lecanemab. We anticipate that this strategy will become standard practice, enhancing patient care by reducing the need for invasive lumbar punctures and their associated costs. Although recent American Appropriate Use Recommendations offer guidance on blood biomarkers for assessing amyloid pathology related to disease-modifying therapy [49], they lack specific cutoffs and a double-threshold approach, and do not differentiate between AD phenotypes, only mentioning AD as a suspected cause of cognitive impairment. Our recommendations address these gaps by specifying common AD phenotypes, implementing a double threshold with at least 97.5 % specificity, and validating biomarkers results through multidisciplinary discussions, thereby ensuring their effective use in clinical practice.

We finally suggest a discontinuation protocol, which aims to facilitate long-term use of lecanemab in the lack of available data, while balancing risk-benefit and treatment burden. This protocol should be updated as additional evidence are available in the future.

As lecanemab gains popularity in the US and becomes covered by Medicare, more data from registries is expected to emerge, allowing for a more precise evaluation of the drug's risk-benefit ratio. Refining the ARIA risk by testing the impact of comorbidities and medications, as well as additional dimensions of cerebrovascular diseases (e.g., CAA

**Table 3**

Appropriate and inappropriate uses of lecanemab in the CLARITY-AD trial and in clinical practice according to American [6] and French recommendations.

	Criteria	CLARITY-AD criteria	American recommendations	French recommendations
<b>Recommended</b>	3.1 Cognitive severity	MMSE score $\geq 22$ and $\leq 30$ at screening and baseline visits	Score compatible with early AD: MMSE 22–30 or another cognitive test	<ul style="list-style-type: none"> <li>- MMSE <math>\geq 22</math>, threshold can be discussed in individuals with low education or language abilities</li> <li>- Autonomy score compatible with early AD can be used in these special situations</li> </ul>
	4.1 Clinical phenotype	Memory impairment (WMS IV - LM II < 1 SD)	Objective impairment in one or more cognitive domains	<ul style="list-style-type: none"> <li>- Amnestic (typical) AD</li> <li>- Other non-amnestic common AD phenotypes (logopenic variant primary progressive aphasia or posterior cortical atrophy)</li> </ul>
	4.1 Biomarkers	Positive biomarker for amyloid pathology (amyloid PET: visual reading or CSF: total tau/A $\beta$ 2 ratio)	Positive amyloid PET or CSF studies indicative of AD	<ul style="list-style-type: none"> <li>- Positive blood biomarker using double threshold (ptau217)</li> <li>- CSF A+/T+</li> <li>- Positive amyloid PET (if inconclusive CSF biomarkers or LP contraindication)</li> </ul>
	6.1 & 6.2 Age	50–90	Physician judgement used for patients outside the 50–90 years age range	<ul style="list-style-type: none"> <li>- No exclusion only based on chronological age</li> <li>- Extreme ages discussed in multidisciplinary meetings</li> <li>- Need for frailty and standardized geriatric assessment for older individuals</li> </ul>
<b>Not recommended</b>	5.1 APOE4 status	Used for subgroup analysis only (efficacy and safety)	APOE genotyping recommended to guide risk discussion and MRI monitoring (supplementary brain MRI scan at week 52)	<ul style="list-style-type: none"> <li>- Need to determine APOE4 status for patient information</li> <li>- Lecanemab not recommended for APOE4 homozygotes</li> <li>- Supplementary MRI monitoring for ARIA for APOE4 heterozygotes</li> </ul>
	10 Antithrombotic agents	Anticoagulant treatment optimized and on a stable dose for 4 weeks	<ul style="list-style-type: none"> <li>- Patients on anticoagulants should not receive lecanemab</li> <li>- tPA should not be administered to individuals on lecanemab</li> </ul>	<ul style="list-style-type: none"> <li>- Lecanemab not recommended for patients on anticoagulants</li> <li>- No absolute contraindication for tPA but need to perform rapid brain MRI to exclude ARIA before use of tPA</li> </ul>
	8 Brain MRI	<ul style="list-style-type: none"> <li>- Brain MRI at screening visit</li> <li>- More than 4 microhemorrhages</li> <li>- A single macrohemorrhage &gt;10 mm</li> <li>- An area of superficial siderosis</li> <li>- Evidence of vasogenic edema</li> <li>- Multiple lacunar</li> <li>- infarcts or stroke involving a major vascular territory</li> <li>- Severe small vessel</li> <li>- Other major intracranial pathology</li> </ul>	<ul style="list-style-type: none"> <li>- Brain MRI within 6 months before lecanemab administration</li> <li>- More than 4 microhemorrhages</li> <li>- A single macrohemorrhage &gt;10 mm</li> <li>- An area of superficial siderosis</li> <li>- Evidence of vasogenic edema</li> <li>- More than 2 lacunar infarcts</li> <li>- Stroke involving a major vascular territory</li> <li>- Severe subcortical hyperintensities (Fazekas 3)</li> <li>- Evidence of ABRA or CAA-ri</li> <li>- Other major intracranial pathology that may cause cognitive decline</li> </ul>	<ul style="list-style-type: none"> <li>- Brain MRI within 6 months before lecanemab administration</li> <li>- More than 4 microhemorrhages (lobar and/or deep)</li> <li>- More than 1 lobar microhemorrhage (probable CAA)</li> <li>- A single macrohemorrhage &gt;10 mm</li> <li>- An area of superficial siderosis</li> <li>- Evidence of vasogenic edema</li> <li>- Multiple lacunar infarcts</li> <li>- Severe white matter hyperintensities (Fazekas score of 3)</li> <li>- Stroke involving a major vascular territory must be evaluated on a case-by-case basis</li> <li>- Other major intracranial pathology that may cause primarily cognitive decline</li> <li>- Unruptured intracranial vascular malformations need to be discussed in multidisciplinary meetings</li> </ul>
<b>To be discussed</b>	7.1 Neurological comorbidities	Any neurological condition that may be contributing to cognitive impairment	Any neurologic condition that may be contributing to the cognitive impairment - Any non-AD MCI or dementia	Multidisciplinary meetings should review comorbid conditions and address the following questions to assess the risk-benefit ratio: <ol style="list-style-type: none"> <li>1) Does the comorbid condition primarily and significantly affect cognition and function despite positive biomarkers?</li> <li>2) Will the comorbid condition likely interfere with the expected safety, magnitude, and temporality of lecanemab's efficacy, thereby impacting its risk-benefit ratio?</li> <li>3) Will the comorbid condition likely affect treatment compliance and monitoring?</li> </ol>
	7.1 Psychiatric comorbidities	Any psychiatric diagnosis or symptoms that could interfere with study procedures	<ul style="list-style-type: none"> <li>- Any psychiatric condition that may be contributing to the cognitive impairment</li> <li>- Patient with mental illness unable to comply with management requirements</li> </ul>	
	7.1 Other medical comorbidities	Any medical conditions not stable	<ul style="list-style-type: none"> <li>- Any medical that may be contributing to the cognitive impairment</li> <li>- Unstable medical conditions</li> </ul>	

Abbreviations: ABRA, Amyloid Beta-Related Angiitis; AD, Alzheimer's Disease; CAA-ri, Cerebral Amyloid Angiopathy-related inflammation; CSF, CerebroSpinal Fluid; MMSE, MiniMental State Examination; PET, Positron Emission Tomography; WMS, Wechsler Memory Scale.

features), will be crucial. Establishing equivalence between microhemorrhage thresholds across MR sequences will also help SWI sequences be used in clinical routine to assess and monitor patients safely on anti-amyloid immunotherapies. Further studies are needed to understand the temporality of ARIA occurrence and the long-term efficacy of lecanemab, including the effect of treatment discontinuation.

Future development of this drug class is expected to include donanemab. However, differences in pharmacodynamics with lecanemab and the use of more complex biomarker investigations in the donanemab phase 3 clinical trial will make it difficult to compare to current guidelines. Therefore, establishing a specific AUR will be necessary.

Implementing lecanemab in the French healthcare system is challenging due to its cost and therapeutic index [3]. If the treatment is approved, it will likely have limited accessibility and be restricted to hospital use. This aligns with the need for a multidisciplinary consultation meeting before initiation, as highlighted in these recommendations. However, the number of eligible patients for lecanemab may exceed the current access capabilities for clinical, biomarker assessment, infusion, and MRI monitoring [3]. The primary factor contributing to the inequity of treatment access will be limited access to specialized diagnosis and infusion centers. Gradually increasing the number of specialized centers will help to reduce these inequities. Additionally, the development of subcutaneous formulations, the emergence of anti-amyloid immunotherapies or titration protocols with better safety profiles, as well as plasma biomarkers, may facilitate the eligibility assessment and monitoring of these drugs, enlarge their indications, and reduce inequities.

As per the EMA Marketing Authorization, a post-authorization safety study must be carried out to characterize ARIA-E and ARIA-H further and assess the effectiveness of the risk minimization measures through an EU-wide registry study with patients treated with lecanemab. This initiative will be similar to the ALZ-NET initiative in the US.

Finally, as data from real-world clinical practice, open-label extension, and other clinical trials keep accumulating, we anticipate these recommendations should be updated regularly.

## 15. Conclusion

Lecanemab treatment requires a comprehensive evaluation of the risk-benefit ratio that should take place in multidisciplinary meetings. In line with the EMA Marketing Authorization, patients with unfavorable risk-benefit profiles (*APOE4* homozygotes, patients on anticoagulants) should not receive lecanemab treatment. We also propose expanding this category to individuals with comorbid probable CAA due to their high risk of amyloid-related ICH until further data become available. We recommend MRI monitoring tailored to *APOE* status and evidence-based temporality of ARIA. Emergency physicians, AD specialists, and radiologists should receive specific training for ARIA management, and early MRI monitoring for ARIA should be performed. Access to lecanemab will require a personalized biological and genetic diagnosis of AD, which is currently not necessary in most cases. To facilitate this implementation, we propose incorporating plasma biomarkers into the eligibility assessment under specific conditions. We also suggest a discontinuation protocol to facilitate long-term use of the treatment. Therefore, in the event of lecanemab approval, the French healthcare system will have to swiftly adapt to these new diagnostic procedures and treatment delivery to ensure equal access for all individuals on the national territory. This will require strengthening collaborations between primary care practitioners and the various levels of Memory Clinics.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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, UCB Pharma, and GE Healthcare SAS; is an unpaid local principal investigator or sub-investigator in NCT04241068 and NCT05310071 (aducanumab, Biogen), NCT05399888 (BIIB080, Biogen), NCT03352557 (gosuranemab, Biogen), NCT05463731 (remternetug, Eli-Lilly), NCT04592341 (gantenerumab, Roche), NCT03887455 (lecanemab, Eisai), NCT03828747 and NCT03289143 (semorinamab, Roche), NCT04619420 (JNJ-63,733,657, Janssen – Johnson & Johnson), NCT04374136 (AL001, Alector), NCT04592874 (AL002, Alector), NCT04867616 (bepranemab, UCB Pharma), NCT04777396 and NCT04777409 (semaglutide, Novo Nordisk), NCT05469360 (NIO752, Novartis), is an unpaid national coordinator for NCT05564169 (masitinib, ABScience), NCT (AD04, Advantage Therapeutics GmbH); has given unpaid lectures in symposia organized by Eisai and the Servier Foundation; has been an unpaid expert for Janssen – Johnson & Johnson.

During the past 3 years, VP was a local unpaid investigator or sub-investigator for clinical trials granted by NovoNordisk, Biogen, Janssen and Alector. Outside this work, he received consultant fees for MRI studies in animals from Motac Neuroscience Ltd and research grants from the Fondation Recherche Alzheimer, Fondation PSP-France and from the Agence Nationale de la Recherche.

During the past 3 years, ML has the following disclosures: 1. Unpaid activities: Investigator or co-investigator for studies by Bayer and Bristol-Myers Squibb laboratories; Participation in the Eisai Symposium on Behavioural Neurology 2023. 2. Paid activities: Consultant for a brochure on Alzheimer's disease Eisai 2024.

CC received personal fees from Bayer (international steering committee member of RCT dedicated to stroke), Biogen (international steering committee member of RCT dedicated to stroke), Boehringer-Ingelheim (board), Novartis (board), Amgen (board), Op2lysis (board). She is Associate Editor of the Stroke Journal. She is a member of data safety monitoring boards (FIVhema, Univ Caen & BLITZ, APHP; unpaid). Her institution receives grant fundings from the ANR, PHRC and France 2030.

MS has served on advisory boards/consultancies Acadia, Otsuka, Avanir, Medesis Pharma, Servier, Eisai, Roche, Biogen, Lilly and Ethypharm.

During the past 3 years, HM has the following disclosures: 1. Unpaid activities: principal investigator or co-investigator in therapeutic trials for the following pharmaceutical groups: NovoNordisk, Biogen, TauRx Pharmaceuticals, Green Valley Pharmaceuticals, EISAI, Roche, Genentech, Lundbeck, Boehringer-Ingelheim, Sanofi, UCB; participation in an EISAI board meeting. 2. Paid activities: EISAI meeting, EISAI regional board, EISAI symposium. 3. Miscellaneous benefits (transport, meals, etc.): Biogen (2022), EISAI (2022, 2023).

During the past 3 years, SB was a local unpaid investigator or sub-investigator for clinical trials granted by Biogen, Roche, Eisai, Eli Lilly, Janssen, Johnson & Johnson, Alector, NovoNordisk, UCB-pharma, Genentech, AB science, Novartis, and GlaxoSmithKline. She received fees from Biogen for a symposium (2021), outside the scope of the submitted work. She received non-personal fees from GE-Healthcare (2023) and Eli-Lilly (2024).

During the past 3 years, JD has received payment/honoraria from Biogen (presentation for Biogen in 2021); and has served as consultant for Roche France in 2020–2022, Eisai France in 2023–2024 and Lilly France in 2024 with personal compensation. He is an investigator in clinical trial sponsored by Regenlife (NCT05926011) and served as consultant and/or SAB member for Regenlife but received no personal compensation.

## CRediT authorship contribution statement

**Nicolas Villain:** Investigation, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Vincent**

**Planche:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Matthieu Lilamand:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Charlotte Cordonnier:** Validation, Writing – review & editing. **Maria Soto-Martin:** Conceptualization, Validation, Writing – review & editing. **Hélène Mollion:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Stéphanie Bombois:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Julien Delrieu:** Investigation, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100094.

### References

- [1] Delrieu J, Andrieu S, Vellas B. Dementia research in 2023: the year of anti-amyloid immunotherapy. *Lancet Neurol* 2024;23(1):13–15.
- [2] van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's Disease. *N Engl J Med* 2023;388(1):9–21.
- [3] Villain N, Planche V, Levy R. 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. *Rev Neurol (Paris)* 2022;178(10):999–1010.
- [4] Sperling RA, Jack CR, 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. *Alzheimers Dement J Alzheimers Assoc* 2011;7(4):367–85.
- [5] Pittock RR, Aakre JA, Castillo AM, Ramanan VK, Kremers WK, Jack CR, et al. Eligibility for anti-amyloid treatment in a population-based study of cognitive aging. *Neurology* 2023;101(19):e1837–49.
- [6] Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis* 2023;10(3):362–77.
- [7] Park KH, Kim GH, Kim CH, Koh SH, Moon SY, Park YH, et al. Lecanemab: appropriate use recommendations by Korean Dementia Association. *Dement Neurocognitive Disord* 2024;23(4):165–87.
- [8] Cohen S, van Dyck CH, Gee M, Doherty T, Kanekiyo M, Dhadda S, et al. Lecanemab clarity AD: quality-of-life results from a randomized, double-blind phase 3 trial in early Alzheimer's disease. *J Prev Alzheimers Dis* 2023;10(4):771–7.
- [9] Planche V, Villain N. Advocating for demonstration of disease modification-have we been approaching clinical trials in early Alzheimer disease incorrectly? *JAMA Neurol* 2023;80(7):659–60.
- [10] Goldberg TE, Lee S, Devanand DP, Schneider LS. Comparison of relative change with effect size metrics in Alzheimer's disease clinical trials. *J Neurol Neurosurg Psychiatry* 2024;95(1):2–7.
- [11] Liu KY, Villain N, Ayton S, Ackley SF, Planche V, Howard R, et al. Key questions for the evaluation of anti-amyloid immunotherapies for Alzheimer's disease. *Brain Commun* 2023;5(3):fcd175.
- [12] [https://www.ema.europa.eu/en/documents/presentation/presentation-section-48-undesirable-effects\\_en.pdf](https://www.ema.europa.eu/en/documents/presentation/presentation-section-48-undesirable-effects_en.pdf).
- [13] Solopova E, Romero-Fernandez W, Harmsen H, Ventura-Antunes L, Wang E, Shostak A, et al. Fatal iatrogenic cerebral  $\beta$ -amyloid-related arteritis in a woman treated with lecanemab for Alzheimer's disease. *Nat Commun* 2023;14(1):8220.
- [14] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc* 2011;7(3):270–9.
- [15] Jack CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc* 2011;7(3):257–62.
- [16] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc* 2011;7(3):263–9.
- [17] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
- [18] Kalafat M, Hugonot-Diener L, Poitrenaud J. Standardisation et étalonnage français du Mini Mental State (MMS) version GRECO. *Revue de Neuropsychologie* 2003;209–36.
- [19] 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* 2023;30(4):414–18.
- [20] Vigliecca NS, Peñalva MC, Molina SC, Voos JA, Vigliecca MR. Is the Folstein's Mini-Mental test an aphasia test? *Appl Neuropsychol Adult* 2012;19(3):221–8.
- [21] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist* 1969;9(3):179–86.
- [22] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56(3):303–8.
- [23] American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. (page 157-158). In.
- [24] Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol* 2014;10(11):634–42.
- [25] Corriveau-Lecavalier N, Botha H, Graff-Radford J, Switzer AR, Przybelski SA, Wiste HJ, et al. Clinical criteria for a limbic-predominant amnesic neurodegenerative syndrome. *Brain Commun* 2024;6(4):fcae183.
- [26] Bergeron D, Gorno-Tempini ML, Rabinovici GD, Santos-Santos MA, Seeley W, Miller BL, et al. Prevalence of amyloid- $\beta$  pathology in distinct variants of primary progressive aphasia. *Ann Neurol* 2018;84(5):729–40.
- [27] Chappelle M, La Joie R, Yong K, Agosta F, Allen IE, Apostolova L, et al. Demographic, clinical, biomarker, and neuropathological correlates of posterior cortical atrophy: an international cohort study and individual participant data meta-analysis. *Lancet Neurol* 2024;23(2):168–77.
- [28] de Souza LC, Corlier F, Habert MO, Uspenskaya O, Maroy R, Lamari F, et al. Similar amyloid- $\beta$  burden in posterior cortical atrophy and Alzheimer's disease. *Brain J Neurol* 2011;134(Pt 7):2036–43.
- [29] Ossenkoppele R, Pijnenburg YAL, Perry DC, Cohn-Sheehy BI, Scheltens NME, Vogel JW, et al. The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. *Brain J Neurol* 2015;138(Pt 9):2732–49.
- [30] Paterson RW, Toombs J, Slattery CF, Nicholas JM, Andreasson U, Magdalinou NK, et al. Dissecting IWG-2 typical and atypical Alzheimer's disease: insights from cerebrospinal fluid analysis. *J Neurol* 2015;262(12):2722–30.
- [31] Ossenkoppele R, Mattsson N, Teunissen CE, Barkhof F, Pijnenburg Y, Scheltens P, et al. Cerebrospinal fluid biomarkers and cerebral atrophy in distinct clinical variants of probable Alzheimer's disease. *Neurobiol Aging* 2015;36(8):2340–7.
- [32] 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 J Neurol* 2021;144(7):2186–98.
- [33] 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(6):484–96.
- [34] Vogel JW, Young AL, Oxtoby NP, Smith R, Ossenkoppele R, Strandberg OT, et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. *Nat Med* 2021;27(5):871–81.
- [35] Qiu Y, Jacobs DM, Messer K, Salmon DP, Feldman HH. Cognitive heterogeneity in probable Alzheimer disease: clinical and neuropathologic features. *Neurology* 2019;93(8):e778–90.
- [36] Planche V, Bouteloup V, Mangin JF, Dubois B, Delrieu J, Pasquier F, et al. Clinical relevance of brain atrophy subtypes categorization in memory clinics. *Alzheimers Dement J Alzheimers Assoc* 2021;17(4):641–52.
- [37] Mattsson-Carlgen N, Grinberg LT, Boxer A, Ossenkoppele R, Jonsson M, Seeley W, et al. Cerebrospinal fluid biomarkers in autopsy-confirmed Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 2022;98(11):e1137–50.
- [38] Ghirelli A, Tosakulwong N, Weigand SD, Clark HM, Ali F, Botha H, et al. Sensitivity-specificity of tau and amyloid  $\beta$  positron emission tomography in frontotemporal lobar degeneration. *Ann Neurol* 2020;88(5):1009–22.
- [39] Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. *Brain J Neurol* 2017;140(12):3329–45.
- [40] Koga S, Josephs KA, Aiba I, Yoshida M, Dickson DW. Neuropathology and emerging biomarkers in corticobasal syndrome. *J Neurol Neurosurg Psychiatry* 2022;93(9):919–29.
- [41] Ossenkoppele R, Smith R, Mattsson-Carlgen N, Groot C, Leuzy A, Strandberg O, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal Alzheimer disease: a head-to-head comparison against amyloid positron emission tomography and magnetic resonance imaging. *JAMA Neurol* 2021;78(8):961–71.
- [42] Townley RA, Graff-Radford J, Mantyh WG, Botha H, Polsinelli AJ, Przybelski SA, et al. Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. *Brain Commun* 2020;2(1):fcaa068.
- [43] Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain J Neurol* 2018;141(7):2181–93.
- [44] Vromen EM, de Boer SCM, Teunissen CE, Rozemuller A, Sieben A, Bjerke M, et al. Biomarker A+T-: is this Alzheimer's disease or not? A combined CSF and pathology study. *Brain J Neurol* 2023;146(3):1166–74.
- [45] Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA* 2011;305(3):275–83.
- [46] Sabri O, Sabbagh MN, Seibyl J, Barthel H, Akatsu H, Ouchi Y, et al. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: phase 3 study. *Alzheimers Dement J Alzheimers Assoc* 2015;11(8):964–74.
- [47] Palmqvist S, Tideman P, Mattsson-Carlgen N, Schindler SE, Smith R, Ossenkoppele R, et al. Blood biomarkers to detect Alzheimer disease in primary care and secondary care. *JAMA* 2024;332(15):1245–57.
- [48] Brum WS, Cullen NC, Janelidze S, Ashton NJ, Zimmer ER, Theriault J, et al. A two-step workflow based on plasma p-tau217 to screen for amyloid  $\beta$  positivity with further confirmatory testing only in uncertain cases. *Nat Aging* 2023;3(9):1079–90.

- [49] Mielke MM, Anderson M, Ashford JW, Jeromin A, Lin PJ, Rosen A, et al. Recommendations for clinical implementation of blood-based biomarkers for Alzheimer's disease. *Alzheimers Dement* 2024;20(11):8216–24.
- [50] Honig LS, Sabbagh MN, van Dyck CH, Sperling RA, Hersch S, Matta A, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. *Alzheimers Res Ther* 2024;16(1):105.
- [51] Reish NJ, Jamshidi P, Stamm B, Flanagan ME, Sugg E, Tang M, et al. Multiple cerebral hemorrhages in a patient receiving Lecanemab and treated with t-PA for stroke. *N Engl J Med* 2023;388(5):478–9.
- [52] 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;178(10):1011–30.
- [53] Zhu XC, Tan L, Wang HF, Jiang T, Cao L, Wang C, et al. Rate of early onset Alzheimer's disease: a systematic review and meta-analysis. *Ann Transl Med* 2015;3(3):38.
- [54] Katzman R. Editorial: the prevalence and malignancy of Alzheimer disease. A major killer. *Arch Neurol* 1976;33(4):217–18.
- [55] 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.
- [56] Salloway S, Farlow M, McDade E, Clifford DB, Wang G, Llibre-Guerra JJ, et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. *Nat Med* 2021;27(7):1187–96.
- [57] Wattmo C, Wallin ÅK. Early- versus late-onset Alzheimer's disease in clinical practice: cognitive and global outcomes over 3 years. *Alzheimers Res Ther* 2017;9. doi:10.1186/s13195-017-0294-2.
- [58] Cho H, Choi JY, Lee SH, Lee JH, Choi YC, Ryu YH, et al. Excessive tau accumulation in the parieto-occipital cortex characterizes early-onset Alzheimer's disease. *Neurobiol Aging* 2017;53:103–11.
- [59] Apostolova LG, Aisen P, Eloyan A, Fagan A, Fargo KN, Foroud T, et al. The Longitudinal early-onset Alzheimer's Disease Study (LEADS): framework and methodology. *Alzheimers Dement J Alzheimers Assoc* 2021;17(12):2043–55.
- [60] Graff-Radford J, Yong KXX, Apostolova LG, Bouwman FH, Carrillo M, Dickerson BC, et al. New insights into atypical Alzheimer's disease in the era of biomarkers. *Lancet Neurol* 2021;20(3):222–34.
- [61] Vanhoutte M, Semah F, Rollin Sillaire A, Jaillard A, Petyt G, Kuchcinski G, et al. 18F-FDG PET hypometabolism patterns reflect clinical heterogeneity in sporadic forms of early-onset Alzheimer's disease. *Neurobiol Aging* 2017;59:184–96.
- [62] Wingo TS, Lah JJ, Levey AI, Cutler DJ. Autosomal recessive causes likely in early-onset Alzheimer disease. *Arch Neurol* 2012;69(1):59–64.
- [63] Joseph-Mathurin N, Llibre-Guerra JJ, Li Y, McCullough AA, Hofmann C, Wojtowicz J, et al. Amyloid-related imaging abnormalities in the DIAN-TU-001 trial of Gantenerumab and Solanezumab: lessons from a trial in dominantly inherited Alzheimer disease. *Ann Neurol* 2022;92(5):729–44.
- [64] Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two randomized phase 3 studies of Aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis* 2022;9(2):197–210.
- [65] Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA* 2023;330(6):512–27.
- [66] Poels MMF, Ikram MA, van der Lugt A, Hofman A, Krestin GP, Breteler MMB, et al. Incidence of cerebral microbleeds in the general population: the Rotterdam Scan Study. *Stroke* 2011;42(3):656–61.
- [67] Feng L, Chu Z, Quan X, Zhang Y, Yuan W, Yao Y, et al. Malnutrition is positively associated with cognitive decline in centenarians and oldest-old adults: a cross-sectional study. *EclinicalMedicine* 2022;47:101336.
- [68] Dyer AH, Murphy C, Segurado R, Lawlor B, Kennelly SP. NILVAD Study Group. Is ongoing anticholinergic burden associated with greater cognitive decline and dementia severity in mild to moderate Alzheimer's Disease? *J Gerontol A Biol Sci Med Sci* 2020;75(5):987–94.
- [69] Wang HF, Zhang W, Rolls ET, Alzheimer's Disease Neuroimaging Initiative, Li Y, Wang L, et al. Hearing impairment is associated with cognitive decline, brain atrophy and tau pathology. *EBioMedicine* 2022;86:104336.
- [70] Beeri MS, Leugrass SE, Delbono O, Bennett DA, Buchman AS. Sarcopenia is associated with incident Alzheimer's dementia, mild cognitive impairment, and cognitive decline. *J Am Geriatr Soc* 2021;69(7):1826–35.
- [71] Jiménez Galán R, Prado-Mel E, Alvarez de Sotomayor M, Martín LAK. Impact of frailty on outcomes of first-line pembrolizumab monotherapy in a real-world population with advanced non-small cell lung cancer. *Biology (Basel)* 2023;12(2):191.
- [72] Ethun CG, Bilen MA, Jani AB, Maithe SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin* 2017;67(5):362–77.
- [73] Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol* 2019;18(2):177–84.
- [74] Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 2012;16(7):601–8.
- [75] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56(3):M146–56.
- [76] Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol* 2023;22(7):602–18.
- [77] Nandigam RNK, Viswanathan A, Delgado P, Skehan ME, Smith EE, Rosand J, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. *AJNR Am J Neuroradiol* 2009;30(2):338–43.
- [78] Assis Lopes P, Raposo N, Charidimou A, Zotin MCZ, Gurol ME, Greenberg S, et al. SWI versus GRE-T2\*: assessing cortical superficial siderosis in advanced cerebral amyloid angiopathy. *Rev Neurol (Paris)* 2023 S0035-3787(23)01138-4.
- [79] Gregoire SM, Werring DJ, Chaudhary UJ, Thornton JS, Brown MM, Youstry TA, et al. Choice of echo time on GRE T2\*-weighted MRI influences the classification of brain microbleeds. *Clin Radiol* 2010;65(5):391–4.
- [80] Greenberg SM, Bacskaï 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(1):30–42.
- [81] Salloway S, Wojtowicz J, Voyle N, Lane CA, Klein G, Lyons M, et al. Amyloid-Related Imaging Abnormalities (ARIA) in Clinical Trials of Gantenerumab in Early Alzheimer Disease. *JAMA Neurol* 2025;82:19–29. doi:10.1001/JAMANEUROL.2024.3937.
- [82] ARIA Insights From Donanemab Trials. Steven M. Greenberg, Paul Ardayfio, Chakib Battioui, Jennifer A. Zimmer, Cynthia D. Evans, Hong Wang, Emel Serap Monkul, Ming Lu, JonDavid Sparks, Scott Andersen, Emily C. Collins, Dawn A. Brooks, John R. Sims. Clinical Trials on Alzheimer's Disease (CTAD) –16th Annual Conference Boston, Massachusetts, USA, and online, October 24 - 27, 2023.
- [83] <https://www.alzforum.org/news/conference-coverage/trontinemab-data-strengthen-hope-brain-shuttles>.
- [84] Charidimou A, Karayiannis C, Song TJ, Orken DN, Thijs V, Lemmens R, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: meta-analysis in stroke patients with AF. *Neurology* 2017;89(23):2317–26.
- [85] Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74(17):1346–50.
- [86] Fandler-Höfler S, Gattringer T, Enzinger C, Werring DJ. Comparison of Boston Criteria v2.0/v1.5 for Cerebral Amyloid Angiopathy to Predict Recurrent Intracerebral Hemorrhage. *Stroke* 2023;54:1901–5. doi:10.1161/STROKEAHA.122.042407.
- [87] Barakos J, Purcell D, Suhy J, Chalkias S, Burkett P, Marsica Grassi C, et al. Detection and management of amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with anti-amyloid beta therapy. *J Prev Alzheimers Dis* 2022;9(2):211–20.
- [88] Jäkel L, De Kort AM, Klijn CJM, Schreuder FFBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. *Alzheimers Dement J Alzheimers Assoc* 2022;18(1):10–28.
- [89] Charidimou A, Boulouis G, Frosch MP, Baron J-C, Pasi M, Albuquer JF, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol* 2022;21:714–25. doi:10.1016/S1474-4422(22)00208-3.
- [90] Bateman RJ, Smith J, Donohue MC, Delmar P, Abbas R, Salloway S, et al. Two phase 3 trials of Gantenerumab in early Alzheimer's disease. *N Engl J Med* 2023;389(20):1862–76.
- [91] Xu H, Xie X, Wang B, Ma S, Wang F. Efficacy and safety of percutaneous left atrial appendage occlusion for stroke prevention in nonvalvular atrial fibrillation: a meta-analysis of contemporary studies. *Heart Lung Circ* 2016;25(11):1107–17.
- [92] VandeVrede L, Gibbs DM, Koestler M, La Joie R, Ljubenkov PA, Provost K, et al. Symptomatic amyloid-related imaging abnormalities in an APOE ε4/ε4 patient treated with aducanumab. *Alzheimers Dement Amst Neth* 2020;12(1):e12101.
- [93] Filippi M, Cecchetti G, Spinelli EG, Vezzulli P, Falini A, Agosta F. Amyloid-related imaging abnormalities and β-Amyloid-targeting antibodies: a systematic review. *JAMA Neurol* 2022;79(3):291–304.
- [94] Moritani T, Hiwatashi A, Shrier DA, Wang HZ, Numaguchi Y, Westesson PLA. CNS vasculitis and vasculopathy: efficacy and usefulness of diffusion-weighted echoplanar MR imaging. *Clin Imaging* 2004;28(4):261–70.
- [95] Mehta A, Isaacson J, Calabria S, Burton SP, Craft VA, Somani S, et al. Amyloid beta-related angitis presenting as multiple cerebral infarcts. *Neuroimmunol Rep* 2023;3:100158.
- [96] Gibson AW, Elser H, Rosso M, Cornblath EJ, Fonkeu Y, Prasad S, et al. Ischemic stroke associated with amyloid-related imaging abnormalities in a patient treated with lecanemab. *Alzheimer's & Dementia* 2024;20:8192–7. doi:10.1002/ALZ.14223.
- [97] Cogswell PM, Barakos JA, Barkhof F, Benzinger TS, Jack CR, Pouissant TY, et al. Amyloid-related imaging abnormalities with emerging Alzheimer Disease therapeutics: detection and reporting recommendations for clinical practice. *AJNR Am J Neuroradiol* 2022;43(9):E19–35.
- [98] Alves F, Kalinowski P, Ayton S. Accelerated brain volume loss caused by anti-β-amyloid drugs: a systematic review and meta-analysis. *Neurology* 2023;100(20):e2114–24.
- [99] Auriel E, Charidimou A, Gurol ME, Ni J, Van Etten ES, Martinez-Ramirez S, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol* 2016;73(2):197–202.
- [100] Regenhardt RW, Thon JM, Das AS, Thon OR, Charidimou A, Viswanathan A, et al. Association between immunosuppressive treatment and outcomes of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol* 2020;77(10):1261–9.
- [101] Antolini L, DiFrancesco JC, Zedde M, Basso G, Arighi A, Shima A, et al. Spontaneous ARIA-like events in cerebral amyloid angiopathy-related inflammation: a multicenter prospective longitudinal cohort study. *Neurology* 2021;97(18):e1809–22.
- [102] Withington CG, Turner RS. Amyloid-related imaging abnormalities with anti-amyloid antibodies for the treatment of dementia due to Alzheimer's disease. *Front Neurol* 2022;13:862369.

- [103] Hecker C, Welponer T, Herold M, Trinka E, Broussalis E, Killer-Oberpfalzer M. Update on treatment strategies for vasculitis affecting the central nervous system. *Drug Discov Today* 2022;27(4):1142–55.
- [104] US FDA OKs monthly maintenance dosing for Eisai/Biogen's Alzheimer's drug | Reuters n.d. <https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-oks-monthly-maintenance-dosing-eisai-biogens-alzheimers-drug-2025-01-26/> (accessed February 21, 2025).
- [105] Ono K, Tsuji M. Protofibrils of amyloid- $\beta$  are important targets of a disease-modifying approach for Alzheimer's disease. *Int J Mol Sci* 2020;21(3):952.
- [106] Nicoll JAR, Buckland GR, Harrison CH, Page A, Harris S, Love S, et al. Persistent neuropathological effects 14 years following amyloid- $\beta$  immunization in Alzheimer's disease. *Brain* 2019;142(7):2113–26.
- [107] van Dyck CH. Anti-amyloid- $\beta$  monoclonal antibodies for Alzheimer's disease: pitfalls and promise. *Biol Psychiatry* 2018;83(4):311–19.
- [108] Alzheimer Therapeutic Program | Brigham and Women's Hospital [Internet]. [cited 2025 Jan 6]. Available from: <https://www.brighamandwomens.org/neurology/cognitive-and-behavioral-neurology/alzheimer-therapeutic-program>.
- [109] Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Agin Health* 2008;4(3):311–20.
- [110] Blaiss MS, Bernstein JA, Kessler A, Pines JM, Camargo CA, Fulgham P, et al. The role of Cetirizine in the changing landscape of IV antihistamines: a narrative review. *Adv Ther* 2022;39(1):178–92.
- [111] Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. *Rheumatology* 2018;57(Supplement\_7):vii54–8.
- [112] Ko D, Pascual-Leone A, Shah SJ. Use of Lecanemab for patients with cardiovascular disease: the challenge of uncertainty. *JAMA* 2024;331(13):1089–90.
- [113] Bilodeau PA, Dickson JR, Kozberg MG. The impact of anti-amyloid immunotherapies on stroke care. *J Clin Med* 2024;13(5):1245.