L'accès aux nouvelles thérapeutiques

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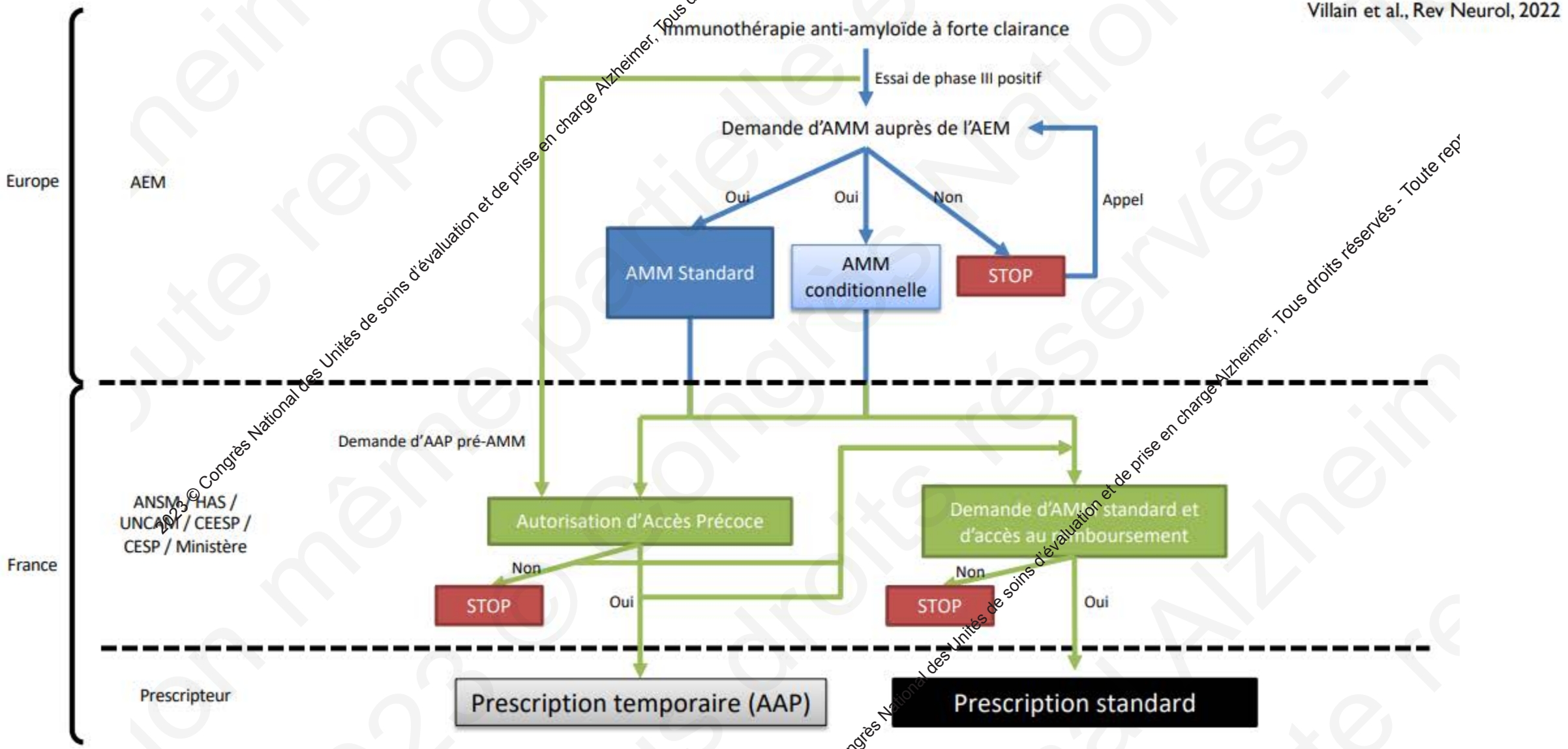
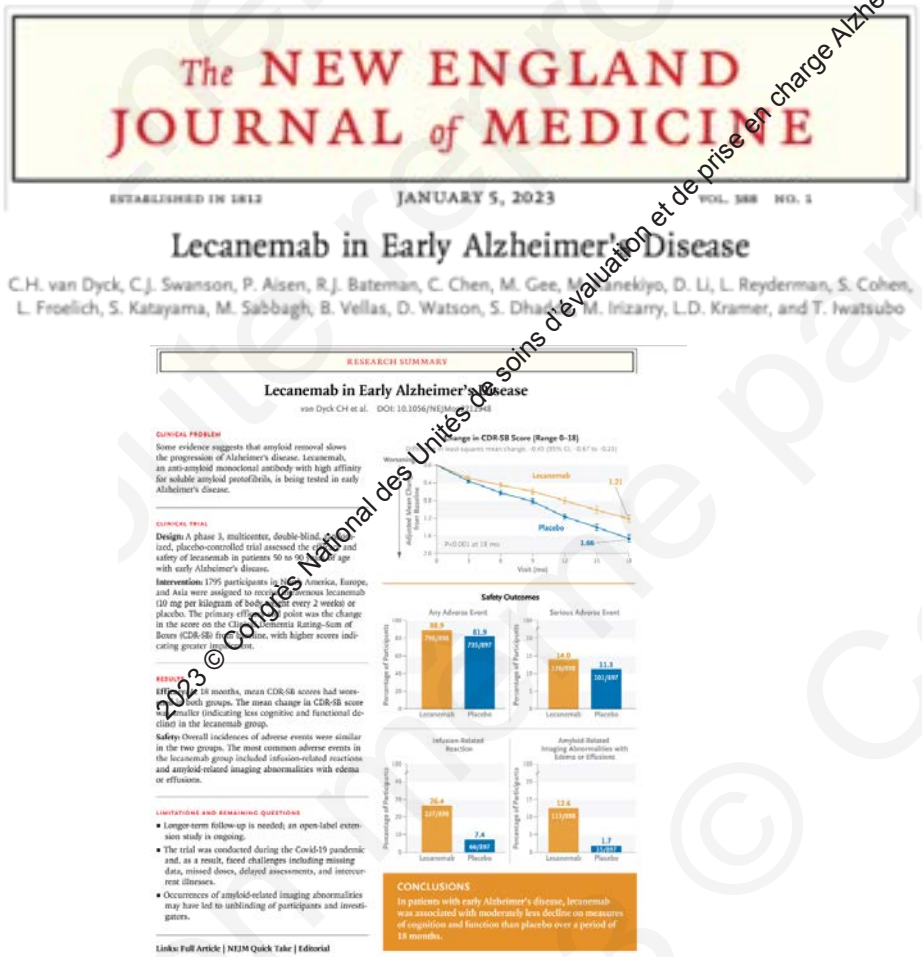


Janvier 2023 : lécanémab



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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

RESEARCH SUMMARY

Lecanemab in Early Alzheimer's Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2212948

CLINICAL PROBLEM

Some evidence suggests that amyloid removal slows the progression of Alzheimer's disease. Lecanemab, an anti-amyloid monoclonal antibody with high affinity for soluble amyloid protofibrils, is being tested in early Alzheimer's disease.

CLINICAL TRIAL

Design: A phase 3, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of lecanemab in patients 50 to 90 years of age with early Alzheimer's disease.

Intervention: 1795 participants in North America, Europe, and Asia were assigned to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary efficacy end point was the change in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) from baseline, with higher scores indicating greater impairment.

RESULTS

Efficacy: At 18 months, mean CDR-SB scores had worsened in both groups. The mean change in CDR-SB score was smaller (indicating less cognitive and functional decline) in the lecanemab group.

Safety: Overall incidences of adverse events were similar in the two groups. The most common adverse events in the lecanemab group included infusion-related reactions and amyloid-related imaging abnormalities with edema or effusions.

LIMITATIONS AND REMAINING QUESTIONS

- Longer-term follow-up is needed; an open-label extension study is ongoing.
- The trial was conducted during the Covid-19 pandemic and, as a result, faced challenges including missing data, missed doses, delayed assessments, and intercurrent illnesses.
- Occurrences of amyloid-related imaging abnormalities may have led to unblinding of participants and investigators.

Change in CDR-SB Score (Range 0–18)

Lecanemab 1.21

Placebo 1.66

Safety Outcomes

Any Adverse Event: Lecanemab 88.9, Placebo 81.9

Serious Adverse Event: Lecanemab 14.0, Placebo 11.3

Infusion-Related Reaction: Lecanemab 26.4, Placebo 7.4

Amyloid-Related Imaging Abnormalities with Edema or Effusion: Lecanemab 12.6, Placebo 1.7

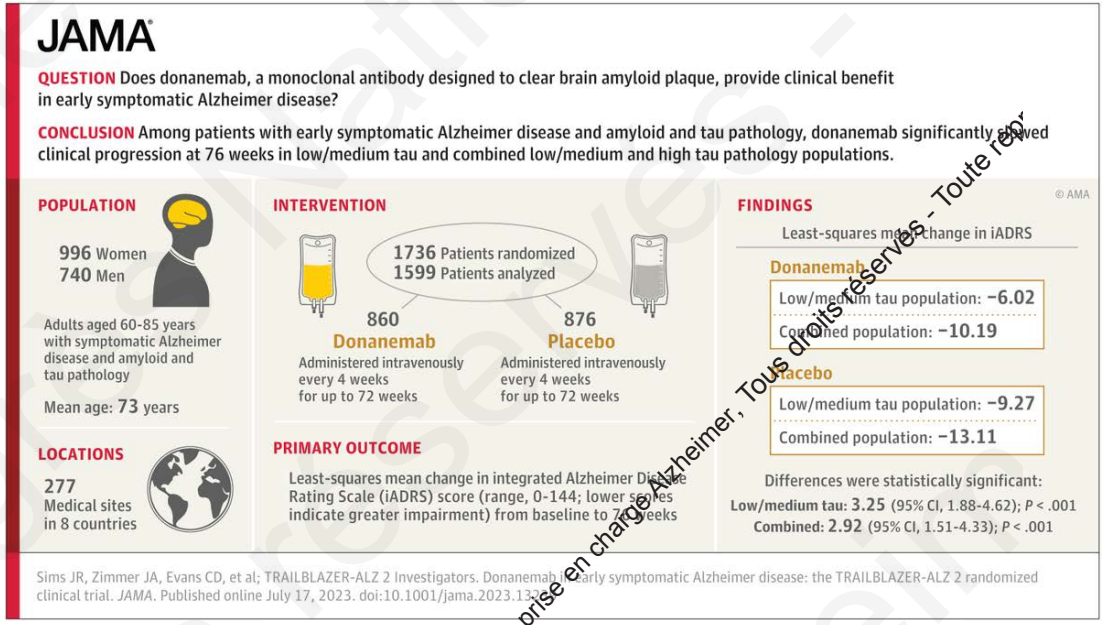
CONCLUSIONS

In patients with early Alzheimer's disease, lecanemab was associated with moderately less decline on measures of cognition and function than placebo over a period of 18 months.

Links: Full Article | NEJM Quick Take | Editorial

6 janvier 2023 : accord accéléré FDA du lécanémab
6 juillet : autorisation traditionnelle USA
Retour EMA imminent …

Juin 2023 : donanémab



JAMA

QUESTION Does donanemab, a monoclonal antibody designed to clear brain amyloid plaque, provide clinical benefit in early symptomatic Alzheimer disease?

CONCLUSION Among patients with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in low/medium tau and combined low/medium and high tau pathology populations.

© AMA

POPULATION

996 Women
740 Men

Adults aged 60-85 years with symptomatic Alzheimer disease and amyloid and tau pathology

Mean age: 73 years

LOCATIONS

277 Medical sites in 8 countries

INTERVENTION

1736 Patients randomized
1599 Patients analyzed

860 **Donanemab**
Administered intravenously every 4 weeks for up to 72 weeks

876 **Placebo**
Administered intravenously every 4 weeks for up to 72 weeks

PRIMARY OUTCOME

Least-squares mean change in integrated Alzheimer Disease Rating Scale (iADRS) score (range, 0-144; lower scores indicate greater impairment) from baseline to 76 weeks

FINDINGS

Least-squares mean change in iADRS

Donanemab
Low/medium tau population: −6.02
Combined population: −10.19

Placebo
Low/medium tau population: −9.27
Combined population: −13.11

Differences were statistically significant:
Low/medium tau: 3.25 (95% CI, 1.88-4.62); $P < .001$
Combined: 2.92 (95% CI, 1.51-4.33); $P < .001$

Sims JR, Zimmer JA, Evans CD, et al; TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. Published online July 17, 2023. doi:10.1001/jama.2023.13239

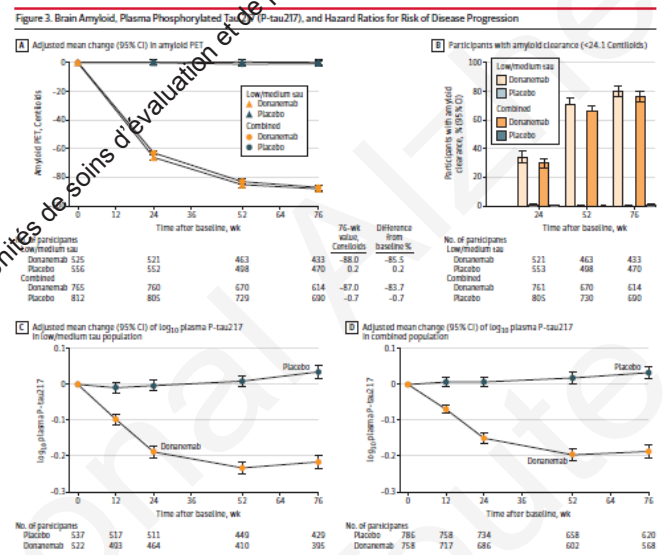


Figure 3. Brain Amyloid, Plasma Phosphorylated Tau (P-tau217), and Hazard Ratios for Risk of Disease Progression

A Adjusted mean change (95% CI) in amyloid PET

B Participants with amyloid clearance (<24.1 Centiloids)

C Adjusted mean change (95% CI) of $\log_{10}$ plasma P-tau217 in low/medium tau population

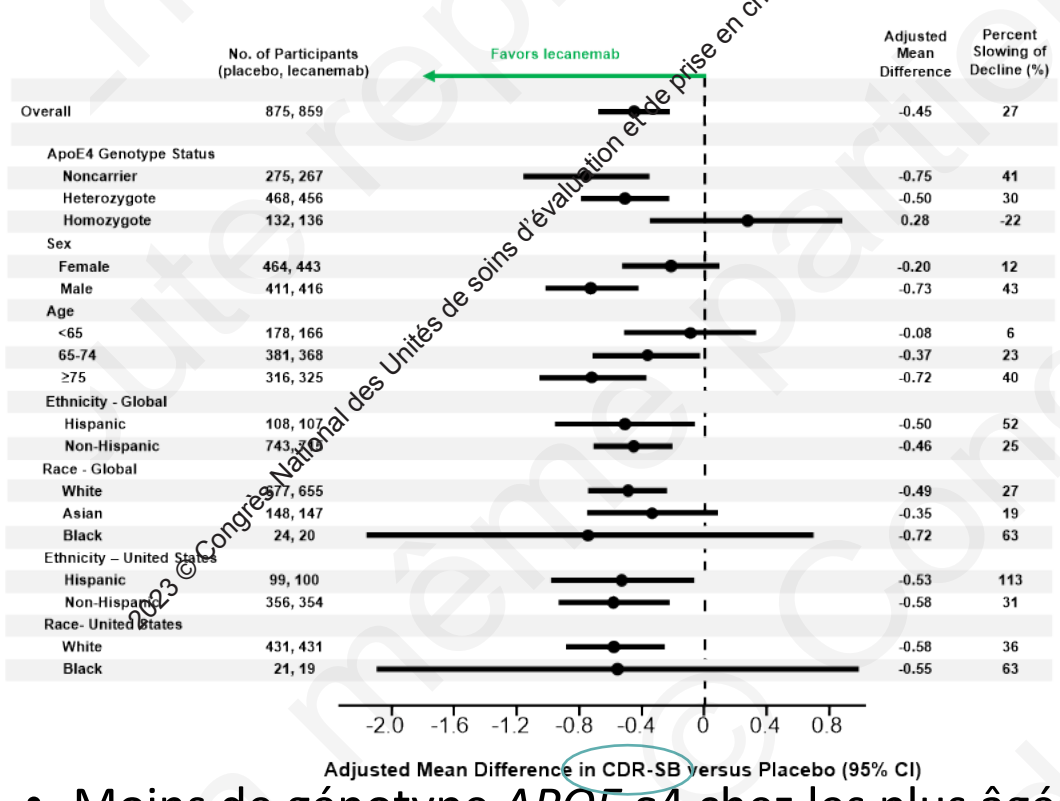
D Adjusted mean change (95% CI) of $\log_{10}$ plasma P-tau217 in combined population

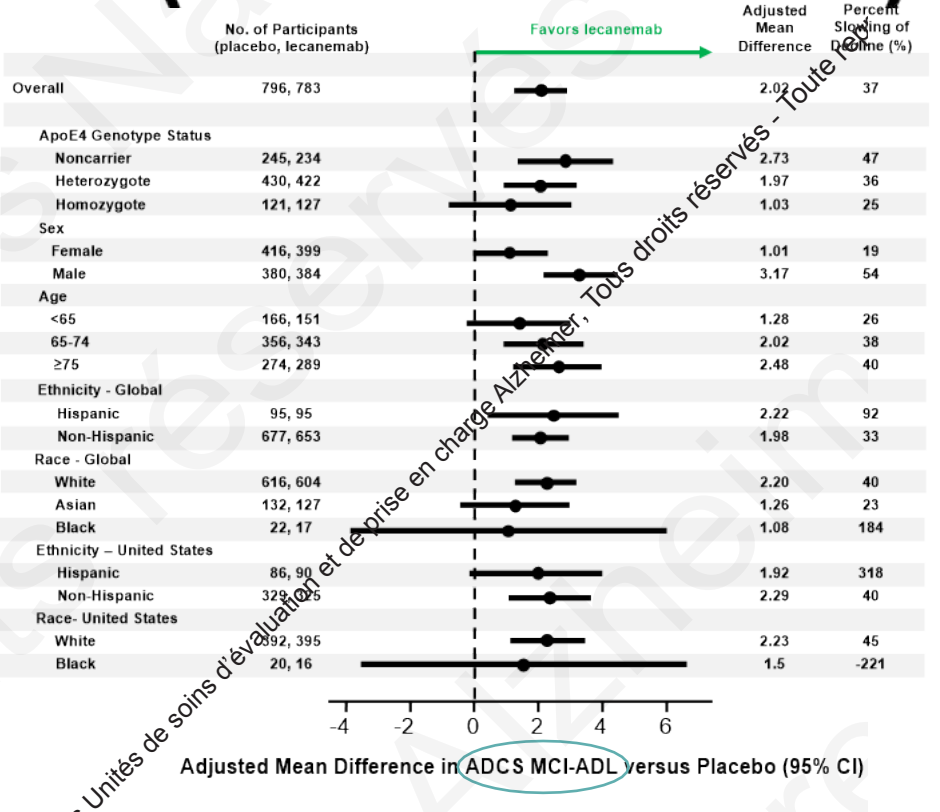
Sous cette hypothèse, quel accès pour quels patients âgés ?
Quels freins et modifications de nos pratiques nécessaires ?

Réflexions au sein du groupe dédié Fédération des Centres Mémoire

Merci :
Maria Soto, Julien Delrieu, Hélène Mollion,
Stéphanie Bombois, Nicolas Villain, Vincent Planche

Efficacité ≥ chez 75+ (CLARITY AD)





- Moins de génotype *APOE* ε4 chez les plus âgés
  - Et dans les populations real-life vs essais cliniques

Van Dyck CH et al. NEJM 2023

Recommandations 2023 lécanémab ➔ questions cruciales *Qui Quand Où Comment*

J Prev Alz Dis 2023;3(10):362-377
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

Lecanemab: Appropriate Use Recommendations

J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group

- TNC léger dû à MA ➔ TNC majeur stade léger (MCI due to AD ➔ Mild dementia)
- Confirmation du statut amyloïde +
- MMSE 22-30
- Age 50-90
- IRM récente indispensable : exclusion patients avec lésions vasculaires (> 4 microbleeds ou > 2 lacunes ou Fazekas III) et surveillance IRM fréquente
- Génotypage ApoE ➔ ε4 associé au risque ARIA

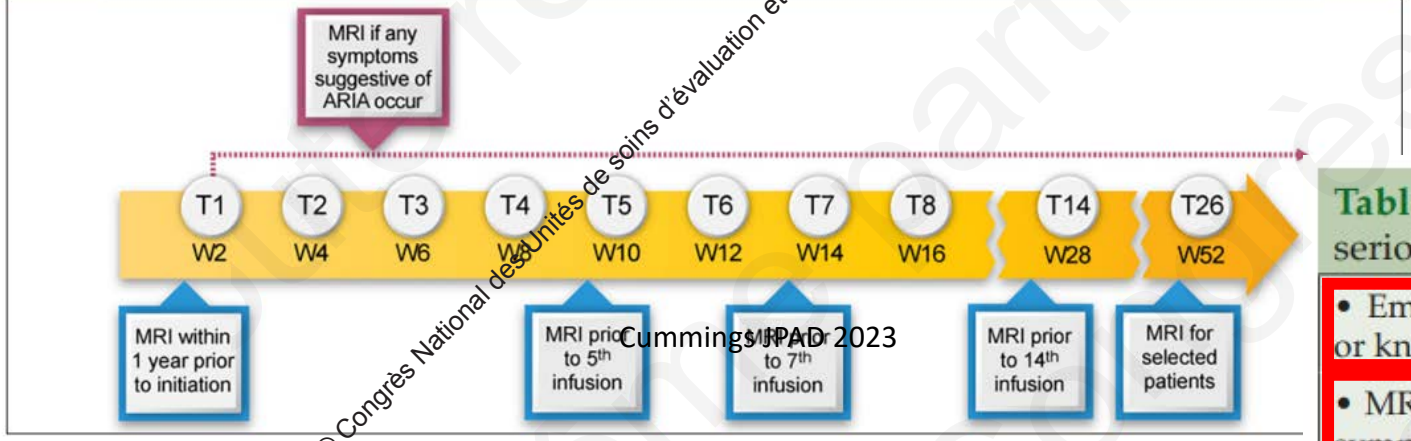
Enjeu n°1 : diagnostic précis et précoce

- **Confirmation du statut A+**
  - Ponction lombaire ou TEP
- **Borne inférieure MMSE = 22** : attention à l'errance diagnostique !
  - Anticiper la première consultation
  - Ne pas banaliser les troubles chez les patients âgés

Enjeu n°2 : infrastructures à adapter

Un monitoring exigeant…

Figure 1. MRI monitoring for lecanemab



Cummings IPAD 2023

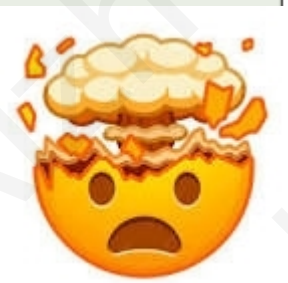
D'importantes ressources nécessaires pour gérer les ARIA…

Table 9. Medical Center resources needed to manage serious or severe ARIA

- Emergency department with resources to assess suspected or known ARIA
- MRI scanners readily available for unscheduled scanning of symptomatic patients
- Knowledgeable MRI readers proficient in detection and interpretation of ARIA
- Clinicians with experience in the management of cerebral edema or ARIA
- Hospital ward for monitoring and management
- Intensive care unit availability
- Electroencephalography available to inpatients
- Neurologist with experience in management of seizures and status epilepticus

Table 11. Resources needed by a clinician or medical center for the safe and effective use of lecanemab

• Clinician skilled in the assessment of cognition to identify individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease
• MRI available for baseline assessment of cerebrovascular pathology and for monitoring of amyloid related imaging abnormalities (ARIA)
• Radiologists, neurologists, or other clinicians expert in the identification and interpretation of cerebrovascular lesions and ARIA
• Amyloid positron emission tomography or lumbar puncture capability to determine the amyloid status of treatment candidates
• Radiologists, nuclear medicine specialists, neurologists, or other specialists skilled in the interpretation of amyloid imaging or neurologists, radiologists, or other clinicians skilled in the conduct of lumbar puncture
• Apolipoprotein E genotyping resources
• Genetic expertise to counsel patients on the implications of apolipoprotein E genotyping
• Expertise in communicating with patients and care partners regarding anticipated benefits, potential harm, and requirements for administration and monitoring while on lecanemab
• Infusion settings that can be made available every two weeks to patients receiving therapy
• Knowledgeable staff at infusion sites capable of recognizing and managing infusion reactions
• Communication channels established between experts interpreting MRIs and clinicians treating patients with lecanemab
• Communication channels established between clinicians treating patients with lecanemab and the patient and care partner
• Availability of hospital resources including intensive care unit
• Expertise in the management of seizures and status epilepticus for patients with severe or serious ARIA
• Protocol with standard operating procedures for management of serious and severe ARIA



Enjeu n°3: critères d'éligibilité stricts pour nos patients de « vraie vie »

RESEARCH ARTICLE

Eligibility for Anti-Amyloid Treatment in a Population-Based Study of Cognitive Aging

Rioghna R. Pittock, Jeremiah A. Aakre, MPH, Anna M. Castillo, MSc, Vijay K. Ramanan, MD, PhD, Walter K. Kremers, PhD, Clifford R. Jack, Jr., MD, Prashanthi Vemuri, PhD, Val J. Lowe, MD, David S. Knopman, MD, Ronald C. Petersen, MD, PhD, Jonathan Graff-Radford, MD,* and Maria Vassilaki, MD, PhD*

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Neurology® 2023;101:e1837-e1849. doi:10.1212/WNL.0000000000207770

Population de la Mayo Clinic Study of Aging avec MA débutante : critères d'exclusion pour lécanémab (A) et aducanumab (B)

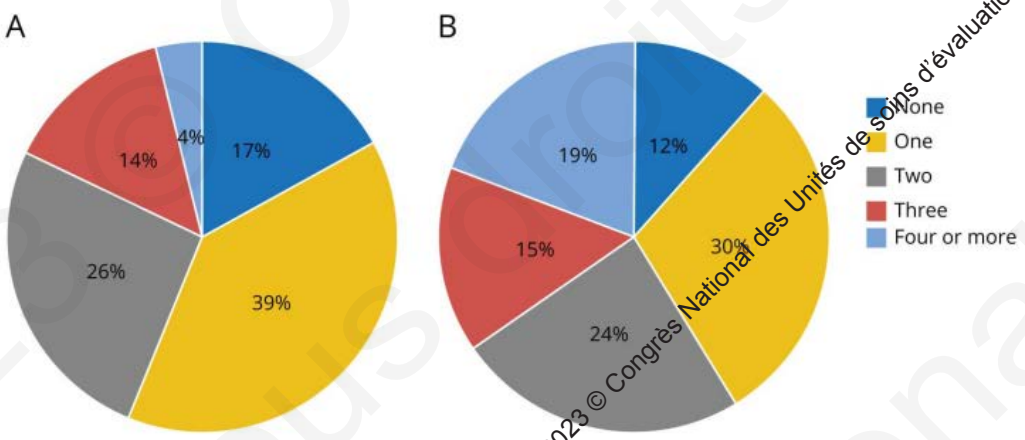


Table 2. Inclusion and exclusion criteria used in the CLARITY AD study and corresponding proposals of the Appropriate Use Recommendations (AUR)

Inclusion and Exclusion Criteria Applied in the Clarity AD Trial of Lecanemab	Appropriate Use Recommendations for Patients Considered for Treatment with Lecanemab
Inclusion Criteria	
Diagnosis of Mild Cognitive Impairment (MCI) or mild AD dementia	Clinical diagnosis of MCI or mild AD dementia as defined in Table 1
Objective impairment in episodic memory, as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII)	Clinical diagnosis of MCI or mild AD dementia as defined in Table 1
Positive biomarker for brain amyloid pathology	Positive amyloid PET or CSF studies indicative of AD
50-90 years of age	Physician judgement used for patients outside the 50-90 year age range
Mini Mental State Examination (MMSE) score > 22 at Screening and Baseline and < 30 at Screening and Baseline	MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD
Body mass index (BMI) greater than (>)17 and less than (<) 35 at Screening	Physician judgement used for patients at the extremes of BMI
If receiving a cholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to Baseline	Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab
Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to Baseline	Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation)
Have an identified study partner	Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab
Provide written informed consent	Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment

Exclusion Criteria	
Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia
More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel; or other major intracranial pathology	More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; more than 2 lacunar infarcts or stroke involving a major vascular territory; severe subcortical hyperintensities consistent with a Fazekas score of 3 (60); evidence of amyloid beta-related angiitis (ABRA); cerebral amyloid angiopathy-related inflammation (CAA-ri); or other major intracranial pathology that may cause cognitive impairment
Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD	MRI evidence of a non-AD dementia
History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening	Recent history (within 12 months) of stroke or transient ischemic attacks or any history of seizures
Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant	Mental illness (e.g, psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements
Geriatric Depression Scale (GDS) score > 8 at Screening	Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates
Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study	Any history of immunologic disease (e.g, lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives
Participants with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5 for participants who are not on anticoagulant treatment, example, warfarin)	Patients with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5 for participants who are not on anticoagulant)
Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose for 4 weeks before Screening	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive lecanemab; tPA should not be administered to individuals on lecanemab
Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments	Unstable medical conditions that may affect or be affected by lecanemab therapy

Enjeu n°4: Génotyper l'APOE

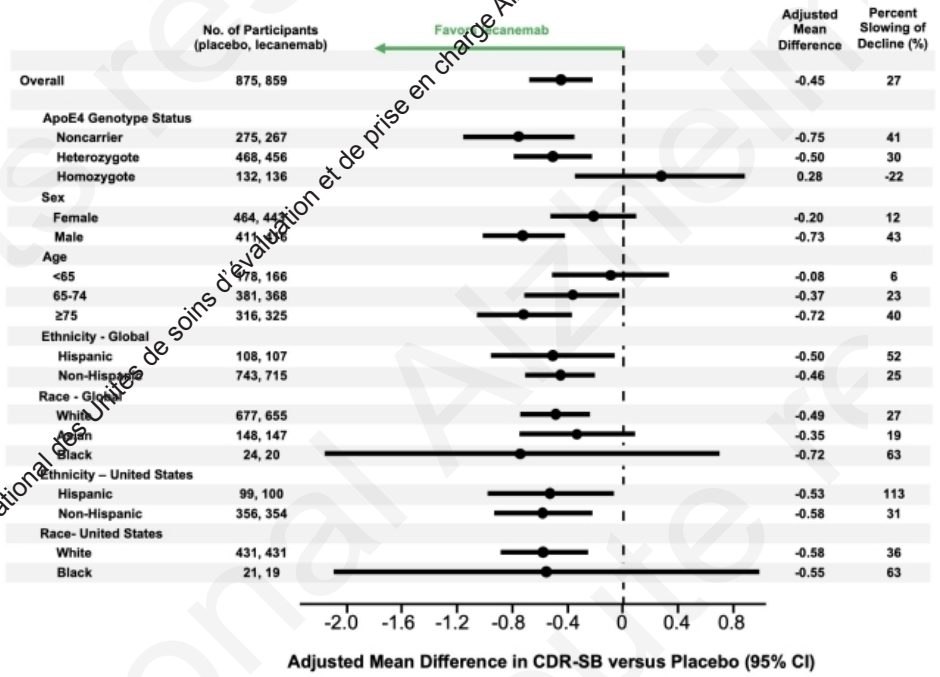
Recommandations relatives au statut APOE

La détermination du statut APOE doit-elle être réalisée dans le bilan pré-thérapeutique ?
Le statut APOE4 est-il une précaution d'emploi à l'utilisation d'une IAA ?

- **Il est recommandé de déterminer le statut APOE en bilan pré-thérapeutique pour discuter la balance bénéfice-risque**
  - Tolérance
  - Efficacité
- **Il est recommandé de ne pas traiter les sujets porteurs homozygotes car la balance bénéfice-risque ne semble pas favorable**
  - E4/E4: FDR d'ARIA-E (x6), d'ARIA-H (x3) et d'ARIA-E symptomatique (x6)
  - ARIA sévères et décès sous lécanémab chez E4/E4

Table 3. (Continued.)

Event	Lecanemab (N=898)	Placebo (N=897)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)



Enjeu n°5 : Parcours et lieu

- **Dépendra du libellé d'AMM**
- **Réunion de concertation pluridisciplinaire** "ouverte" : recommandation d'une **RCP systématique** (clinicien CMRR, neuroradiologue, +/- neuropsychologue, +/- médecin nucléaire, +/- biologiste) -> indications, surveillance, à visée pédagogique, ...

- **Lieu d'administration IAA**
  - Non restreinte à une labélisation de la consultation "Mémoire" mais plutôt à la disponibilité de ressources
    - Centres qui participent à la base de données BNA : recommandé
    - Plateau technique - notamment IRM, … : recommandé

- CMRR : recommandé
- Consultations territoriales : en fonction du plateau technique et BNA
- Consultations de proximité : en fonction du plateau technique et BNA

- Domicile : non recommandé dans un premier temps (à discuter dans un second en SC)

Parcours (du combattant)

Patients âgés avec MA clinique

Souhait d'une IAA

Diagnostic confirmé par BM

Génotypage
Critères d'exclusion

Stade suffisamment précoce

EVALUATION GERIATRIQUE STANDARDISEE

RCP en CMRR

Conclusion et perspectives 2023

sous réserve des aspects réglementaires / conditions de l'AMM

- **Des parcours à penser !**
- Changements majeurs dans le **diagnostic : biomarqueurs, génotypage**
- Nécessité de **formation de tous les acteurs** : neurologues, gériatres, radiologues, urgentistes, neuropsy, IDE, … aidants et patients
- Infrastructures dédiées : HDJ, IRM, lits USINV disponibles
- Registre de **surveillance des ARIA et effets indésirables**
- Recommandations nationales en cours