Donanemab approved for early symptomatic Alzheimer's disease

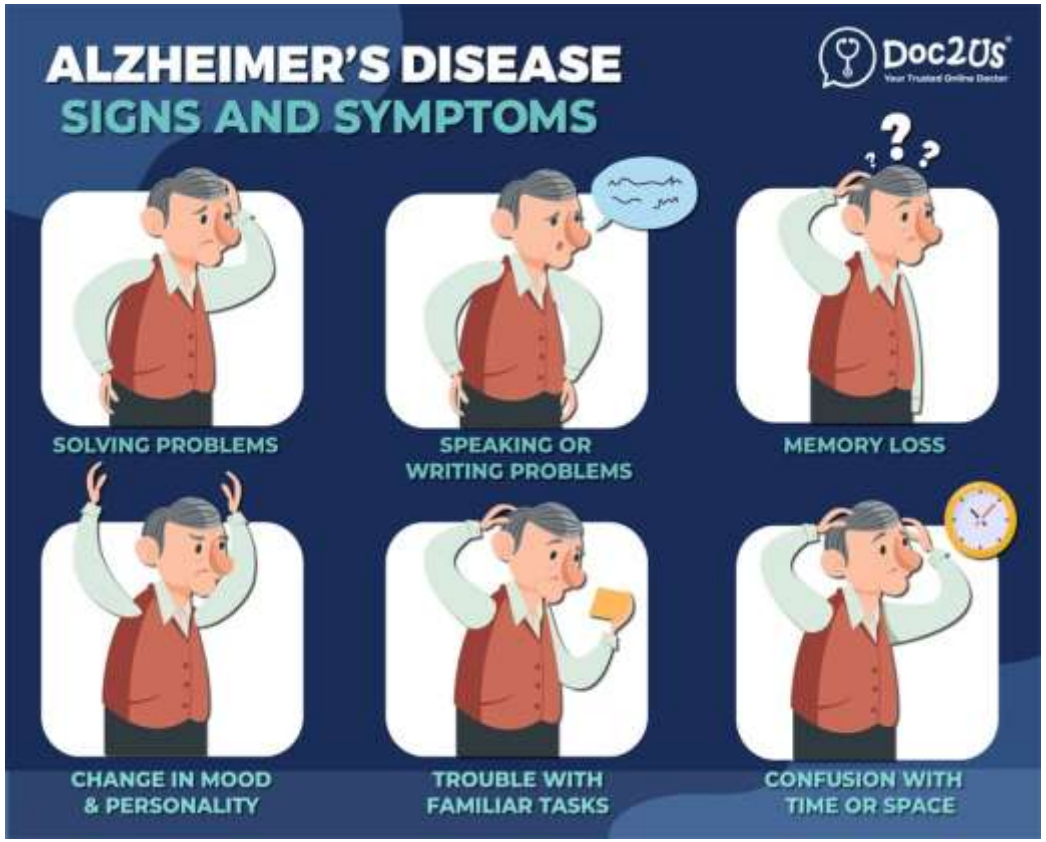
By:

MSc student Roaa Tahseen

Clinical Pharmacy

Alzheimer disease

- Is a progressive illness of unknown cause characterized by loss of cognitive and physical functioning, commonly with behavior symptoms.
- Is a devasting disease affecting an estimated 50 million people worldwide.
- It is estimated that the number will reach **152** million in **2050**.

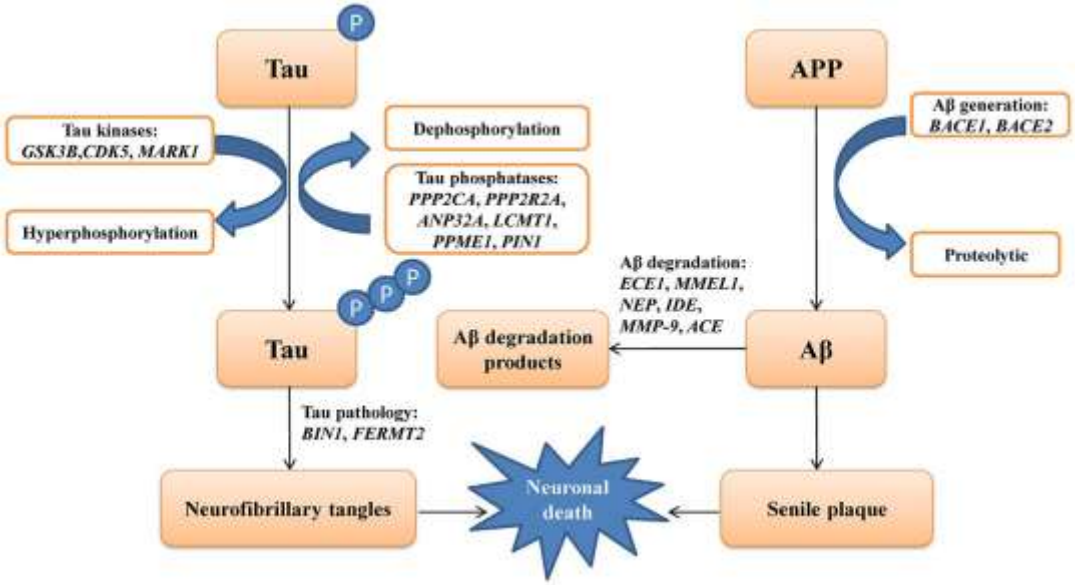


Pathophysiology of Alzheimer's disease

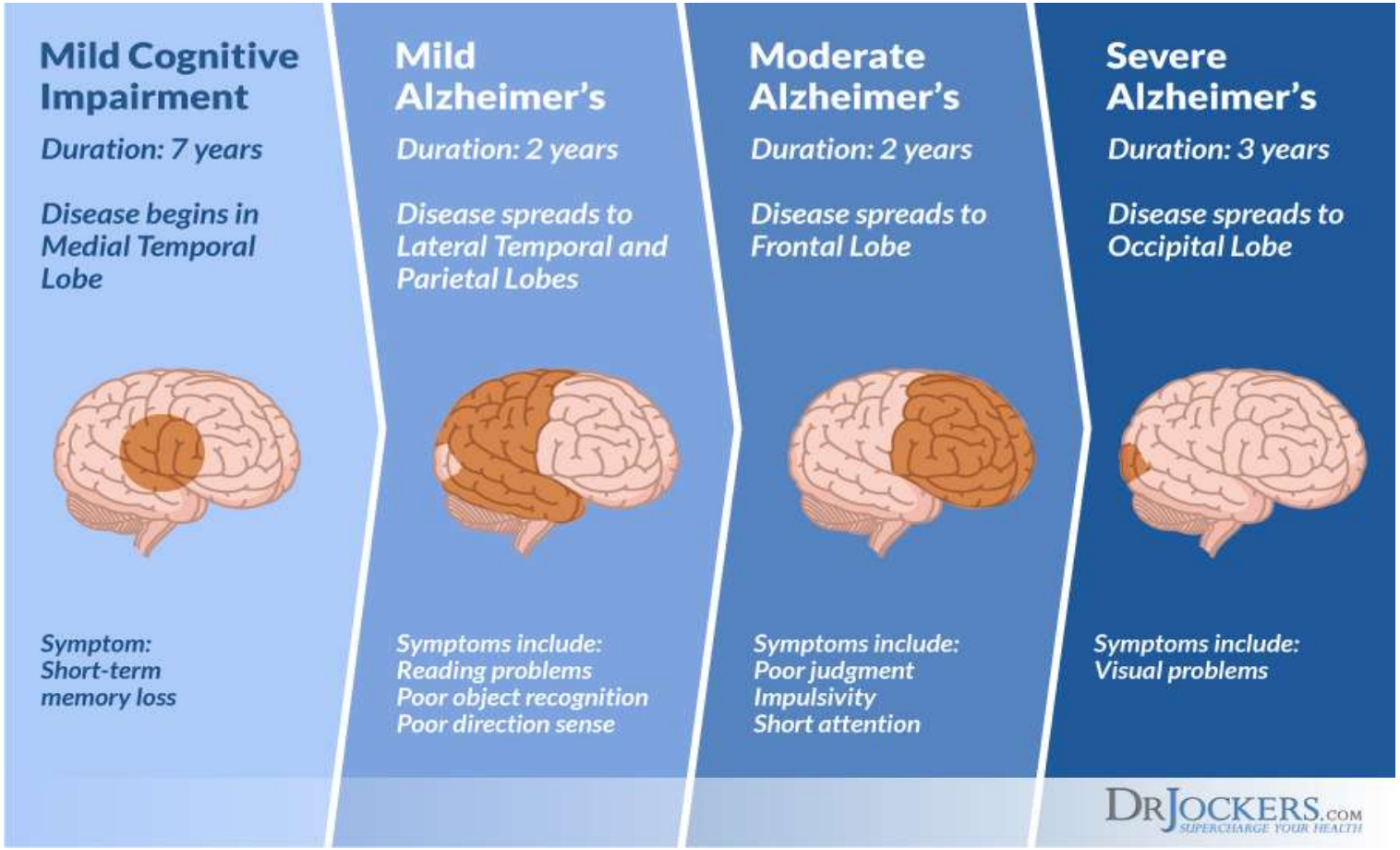
- The pathophysiology of AD has not yet been fully elucidated, and there are various descriptive hypotheses:
- 1- **The amyloid/Aβ hypothesis** (amyloid β is overproduced and aggregates to form amyloid plaques).
- 2- **Tau propagation hypothesis** (Tau proteins are over phosphorylated and then misfold to form neurofibrillary tangles).
- Cholinergic hypothesis, calcium homeostasis hypothesis, neurovascular hypothesis, and inflammatory hypothesis, etc.

Pathophysiology of Alzheimer's disease

❖Currently, most academics believe that Aβ plays a pivotal role in the pathogenesis of AD, and the main research focused on decreasing Aβ as a key player in AD development and progression.



Stages of AD


Mild Cognitive Impairment
Duration: 7 years
Disease begins in Medial Temporal Lobe
Symptom: Short-term memory loss
Mild Alzheimer's
Duration: 2 years
Disease spreads to Lateral Temporal and Parietal Lobes
Symptoms include: Reading problems Poor object recognition Poor direction sense
Moderate Alzheimer's
Duration: 2 years
Disease spreads to Frontal Lobe
Symptoms include: Poor judgment Impulsivity Short attention
Severe Alzheimer's
Duration: 3 years
Disease spreads to Occipital Lobe
Symptoms include: Visual problems
DrJockers.com
SUPERCHARGE YOUR HEALTH

Treatment of AD

❖ Goals of Treatment: To maintain cognitive functioning and activities of daily living as long as possible, with a secondary goal to treat the psychiatric and behavioral symptoms.

❖ **Pharmacologic Therapy of Cognitive Symptoms**

❑ **Cholinesterase Inhibitors:**

- Donepezil, rivastigmine, and galantamine are indicated in mild to moderate AD.
- Donepezil is also indicated for severe AD. No trials have assessed the effectiveness of one agent over another.

Treatment of AD

❑NMethyl DAspartate (NMDA) Receptor Antagonist

- Memantine is used as monotherapy and in combination with a cholinesterase inhibitor and is indicated for moderate to severe AD, but not for mild AD.

- Memantine may help mitigate some of the GI effects seen with cholinesterase inhibitors.

Treatment of AD

❑Anti-amyloid Monoclonal Antibody

- Four humanized immunoglobulin G1 mAbs have been designated as AD breakthrough therapies by the FDA (ie, aducanumab, lecanemab, and donanemab).

- Aducanumab was controversially approved for use in MCI due to AD and mild AD.

Treatment of AD

❖Pharmacologic Therapy of Neuropsychiatric Symptoms

- No medication is FDA-approved for the treatment of AD behavioral and psychological symptoms of dementia (BPSD).
- Cholinesterase inhibitors and memantine may be beneficial in treating BPSD, but they do not reduce acute agitation. Avoid anticholinergic medications as they may worsen cognition.
- **Antidepressants** may help manage anxiety, apathy, as well as agitation and aggression.
- **Antipsychotic medications** have traditionally been used for psychotic and hyperactive symptoms

Donanemab for the Treatment of AD

- July 2018 and June 2021: Fast Track and Breakthrough Therapy designations based on the potential to treat a serious condition and offer a substantial improvement over available therapy.
- May 2022: submission for Accelerated Approval based on the registration-quality Phase 2 study (TRAILBLAZER-ALZ; AACG)

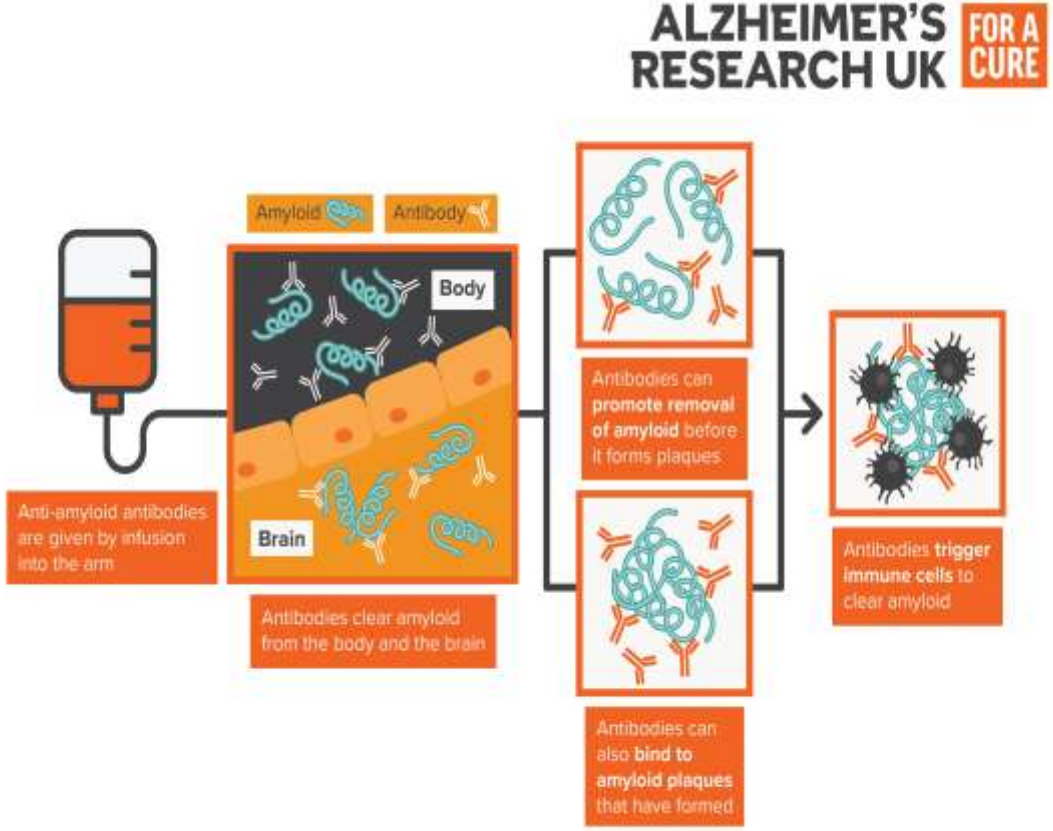
Donanemab for the Treatment of AD

- January 2023: Complete Response due to lack of sufficient 1-year exposures; no other deficiencies were noted.
- June 2023: Class 2 Resubmission for traditional approval, based on the Phase 3 study (TRAILBLAZER-ALZ 2; AACI).
- October 2023: Major Amendment for additional FDA review time of newly requested safety analyses.
- 2 July 2024: the FDA approved the marketing authorization for Kisunla (donanemab) for adults with early symptomatic Alzheimer's disease (AD).

Donanemab for the Treatment of AD

❑Mechanism of action

- Donanemab is a monoclonal antibody specific for an insoluble form of amyloid beta present only in brain amyloid plaques, known as N-truncated pyroglutamate amyloid beta.
- Donanemab binds to the deposited amyloid plaque and aids its removal through microglial-mediated phagocytosis.



Donanemab for the Treatment of AD

- Unlike currently available treatments, which can only relieve symptoms, donanemab is a so-called '**disease-modifying' treatment.** It is designed to tackle the underlying disease.

Donanemab for the Treatment of AD

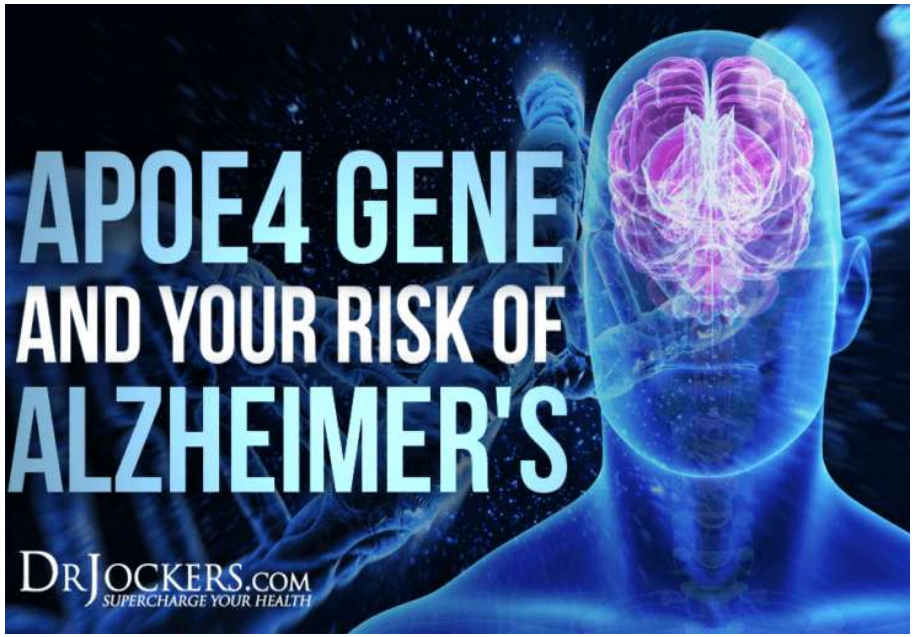
❑Proposed indication

- Donanemab has been designed for people in the early stages of Alzheimer's disease. It is only available for people with a diagnosis of mild Alzheimer's disease or mild cognitive impairment (MCI) with evidence of amyloid buildup in the brain. This must be confirmed by a spinal fluid test (lumbar puncture) or a PET brain scan.
- Many experts suspect donanemab would be unlikely to work in the later stages of Alzheimer's disease, when levels of tau tend to be higher, although this hasn't been tested in trials yet.

Donanemab for the Treatment of AD

❑Proposed contraindications

- People with a suitable diagnosis and amyloid in their brains will also have a genetic test to look for the APOE4 gene. People with two copies of APOE4 are at higher risk of developing side effects, like brain swelling and bleeds (known as ‘ARIA’). They will not be eligible for the drug due to safety concerns.



Donanemab for the Treatment of AD

- People with cerebral amyloid angiopathy are not suitable for donanemab due to safety concerns.

- Similarly, people taking anticoagulants are not suitable for donanemab due to an increased risk of brain swellings and bleeds.

Donanemab for the Treatment of AD

❑Proposed dosing regimen

- Administer 700 mg via intravenous infusion every four weeks for the initial three doses, subsequently increase to 1400 mg every four weeks, with cessation possible upon clearance of brain amyloid plaques.

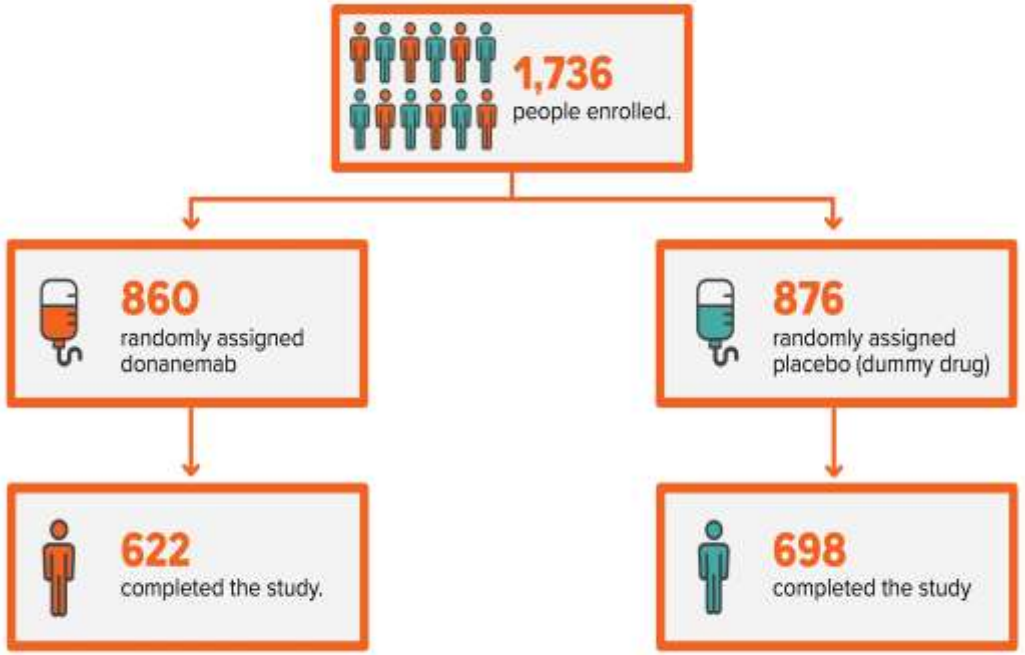
Donanemab for the Treatment of AD

❑Efficacy of donanemab

- Lilly's TRAILBLAZER ALZ-2 clinical trial showed that donanemab slowed the decline in symptoms over a year. This included memory, thinking, and ability to carry out daily activities.
- The international trial included over 1,700 participants with early Alzheimer's disease. It tested donanemab against a dummy drug (placebo) to see how well it worked at slowing down the progression of the disease and whether it was safe.

Donanemab for the Treatment of AD

- Unlike lecanemab, people are not required to continue taking donanemab once it has cleared the protein amyloid from the brain. This means that so far, people taking donanemab do not need to stay on the drug for extended periods of time. In trials, almost half of people taking donanemab were able to stop taking the drug within a year.



Donanemab for the Treatment of AD

- Once this had happened participants were switched to the placebo for the rest of the trial.
- After one year participants were tested against several measures of memory and thinking, and again at eighteen months.

❖**Key results**

- Donanemab reduced memory and thinking decline by 35% in individuals with low-medium levels of tau protein compared to placebo.

Donanemab for the Treatment of AD

- The symptoms of almost half (47%) of those on donanemab did not get significantly worse over a year on the drug, compared with 29% on placebo.
- In people with low-medium levels of tau the drug also resulted in 40% less worsening in the ability to perform everyday activities, like managing finances, driving and carry out hobbies.
- Donanemab had no significant effect in people with **high levels of tau**.
- Finally, participants on donanemab had a 39% lower risk of progressing to the next stage of disease compared to placebo over 18 months.

Donanemab for the Treatment of AD

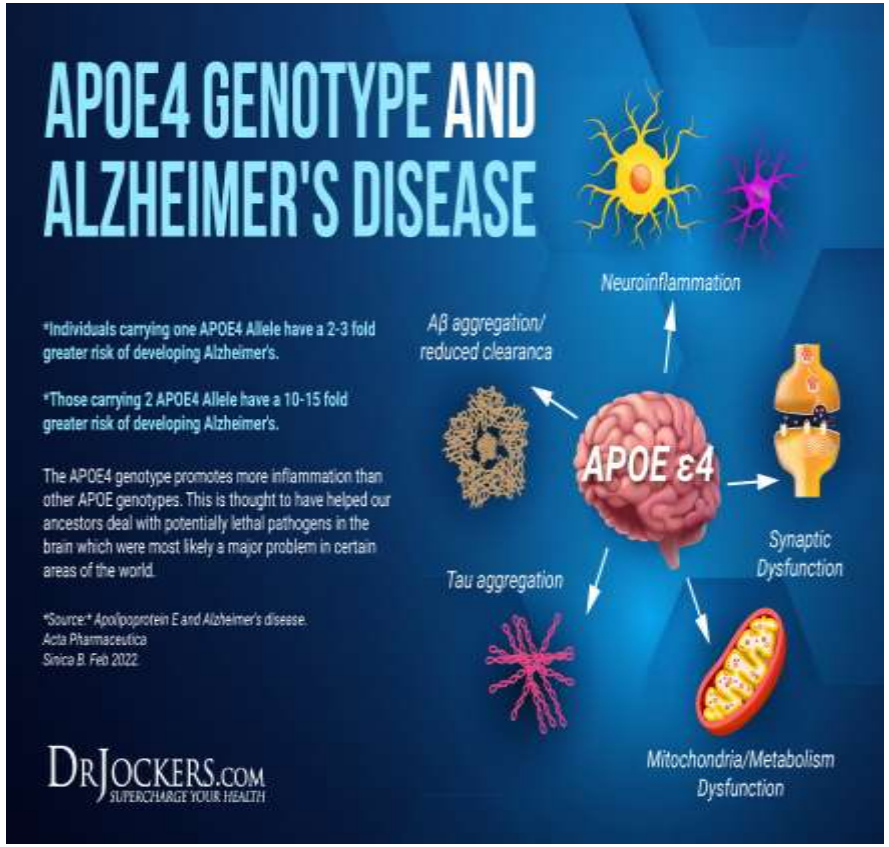
❑Safety of donanemab

- **Amyloid-related imaging abnormalities:**

- It is hypothesized that anti-Aβ antibodies accelerate the breakdown and clearance of Aβ, which may disrupt vascular integrity and result in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI:–
- ARIA-E (edema): vasogenic edema or sulcal effusions
- ARIA-H (hemosiderin deposition): microhemorrhage or superficial
- siderosis.

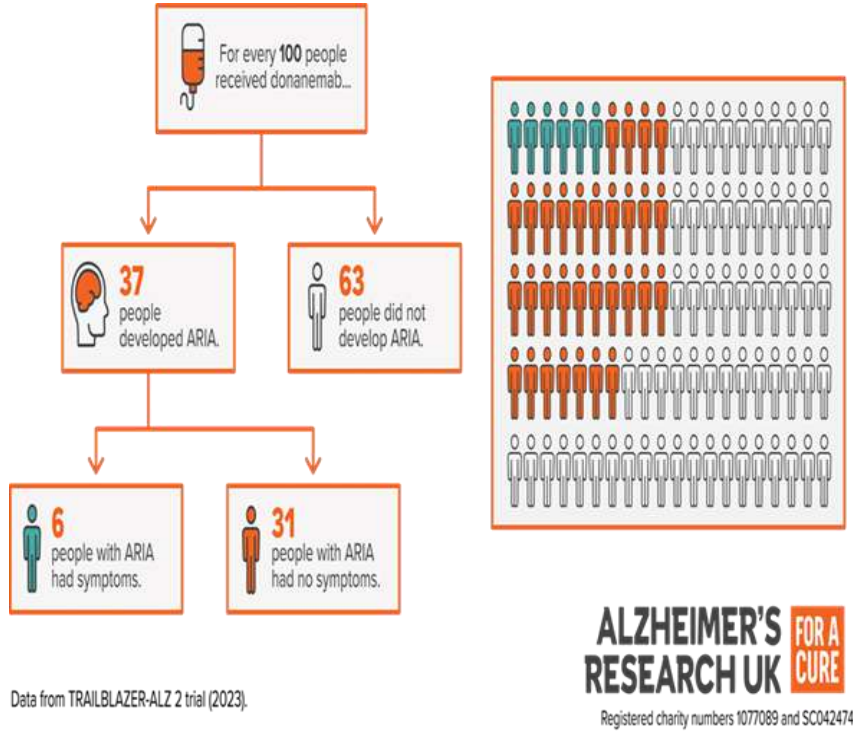
Donanemab for the Treatment of AD

- In the general population two in every100 people inherit two copies of APOE4. As the gene increases our risk of developing Alzheimer's, 15 in every 100 people with the condition have two copies.



Donanemab for the Treatment of AD

- People with two copies of APOE4 are more likely to experience ARIA. In the TRAILBLAZER-ALZ 2 trial, around eight in 20 people with two copies of the APOE4 developed brain swelling (ARIA-E) compared to three in every 20 people with no copies of APOE4 on donanemab.



Donanemab for the Treatment of AD

- **ARIA Management**
- Based on the learnings about ARIA, including the three fatal ARIA-related cases from the clinical trials, recommendations for managing ARIA include the following:

➢Labeling identifying patients at increased risk for ARIA, including testing for APOE4 status as well as those with baseline MRI findings consistent with cerebral amyloid angiopathy.

➢Dose titration as part of standard dose posology.

Donanemab for the Treatment of AD

- Monitoring MRI scans early in treatment with assessments prior to the second, third, fourth, and seventh infusion and for any symptomatic ARIA.

Donanemab for the Treatment of AD

- Dose interruption for radiographically moderate or severe, symptomatic or serious ARIA, and reassessment of benefit-risk:
  - resume dosing after resolution or stability of MRI and symptoms (if present) or
  - permanent discontinuation of donanemab.
- Use of **corticosteroids** as appropriate for serious or symptomatic ARIA.

Donanemab for the Treatment of AD

- **Infusion-related reactions:**
- In donanemab-treated patients, IRRs were commonly observed (8.5%), and anaphylaxis was uncommonly observed (0.3%).
- Most of the IRRs were mild or moderate in severity (94%), occurred during the infusion or within 30 minutes and resolved the same day.
-

Donanemab for the Treatment of AD

- The most common signs and symptoms of IRRs were erythema, nausea or vomiting, chills, and sweating.

- Most patients experiencing an IRR reported an event within or by the fourth infusion

Donanemab for the Treatment of AD

- **IRR Management**
- IRR was managed through close monitoring, slowing infusions, and supportive therapy, with 67% of events not requiring any therapy, often using diphenhydramine or paracetamol.
- On subsequent infusions, around 40% of patients had an IRR, whether they received prophylaxis or slowed the infusion on rechallenge, and 60% did not have an IRR.
- A slower infusion or use of prophylaxis did not reduce the chance of an IRR upon rechallenge.

Donanemab for the Treatment of AD

- **Serious hypersensitivity** can be managed through warning language in labelling, monitoring during infusion, and observing for at least 30 minutes post-infusion, providing symptomatic therapy when needed. Contraindications should be followed to ensure patients with known serious hypersensitivity to donanemab or excipients do not initiate donanemab treatment.

Will donanemab work on other types of dementia, such as vascular dementia or dementia with Lewy bodies?

- At the moment donanemab is only intended for people with Alzheimer's disease. That's because it targets amyloid, which scientists believe plays an important role in the development of Alzheimer's. It is not thought to be as important in other types of dementia, so it is unlikely to work against other diseases that cause dementia.

Top-line differences between aducanumab, lecanemab, and donanemab

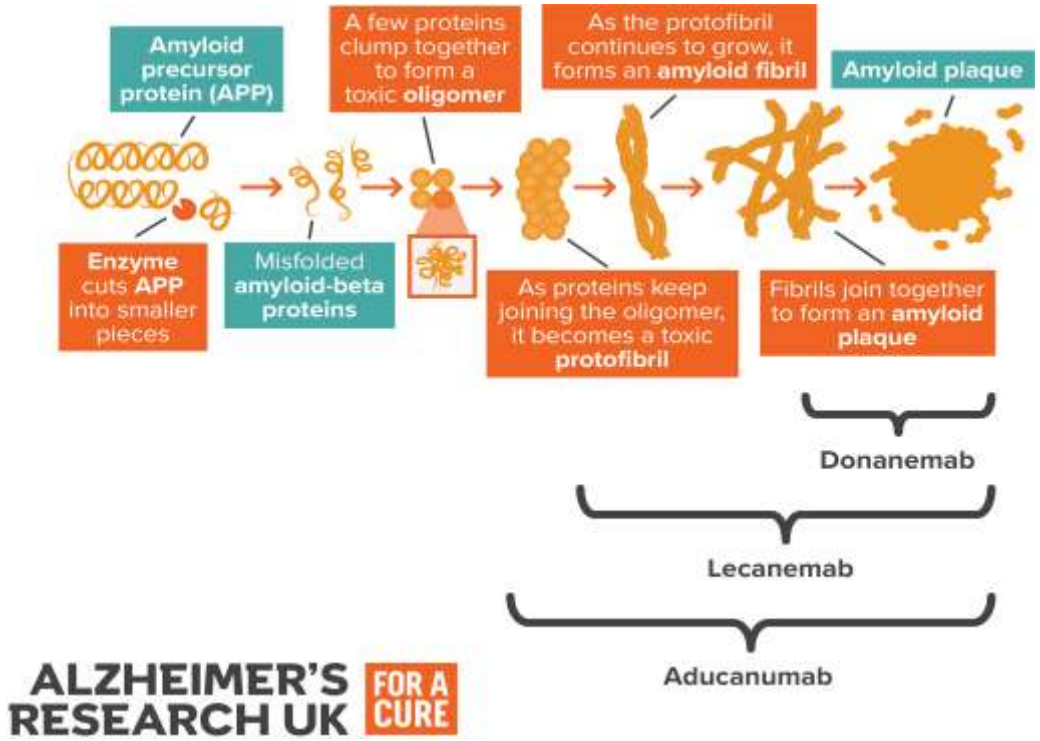
❑FDA approval

- In 2021, the FDA approved **aducanumab.**
- The FDA approved **Lecanemab** in January 2023
- And **donanemab** was approved on 2 July 2024.

Top-line differences between aducanumab, lecanemab, and donanemab

❑Mechanism of action

- **Aducanumab** acts on both soluble forms and established plaques
- **Lecanemab** targets earlier-stage soluble amyloid aggregates.
- **Donanemab** binds to insoluble pyroglutamate-modified amyloid-beta plaques, promoting their clearance.



Top-line differences between aducanumab, lecanemab, and donanemab

❑Mode of Administration

- All three drugs are given as intravenous infusions based on the patient's weight:

- **lecanemab** is given every 2 weeks, while **aducanemab** and **donanemab** are given every 4 weeks.

Top-line differences between aducanumab, lecanemab, and donanemab

❑Efficacy

- **Aducanemab** demonstrated a 22% reduction in cognitive decline at high doses.
- **Lecanemab** trial show that it reduces the rate of Alzheimer's disease by 27%.
- **Donanemab** slowed cognitive and functional decline in Alzheimer's patients by 35%,
- Donanemab is **more effective** than both aducanumab and lecanemab in reducing cognitive decline.

Top-line differences between aducanumab, lecanemab, and donanemab

❑Onset of action:

- According to **aducanumab** clinical trials, it takes ~18 months to reduce amyloid plaque levels.
- **Lecanemab's** Phase 3 trial, amyloid reduction is achieved within 3 months of treatment and clinical benefits within 6 months of treatment. In the research, more than 80% of subjects were amyloid negative (by visual reading) within 12–18 months of treatment in comparison to the placebo treatment.
- **Donanemab** resulted in a decrease of amyloid plaque by 24 weeks, and 68% of those who received donanemab were "amyloid-negative" — meaning their amyloid plaque level was below 24.1 CL (complete amyloid clearance) — by the 76-week mark.

Top-line differences between aducanumab, lecanemab, and donanemab

❑Safety

- In **aducanumab** trials, 41% of participants experienced ARIA, primarily ARIA-E.
- In the phase 3 trials, the reported rates of ARIA were slightly higher for **donanemab** (ARIA-E 24.0%, ARIA-H 31.4%) compared to **lecanemab** (ARIA-E 12.6%, ARIA-H 17.3%).
- Thus, lecanemab may present the least risk for ARIA among these treatments.

References

- 1-Salloway S, Pain A, Ferguson MB, et al. TRAILBLAZER-ALZ 4: Directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease – results from 18 months. Abstract presented at Symposium: 18th International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders (AD/PD); March 05 09, 2024; Lisbon, Portugal.
- 2-Antolini L, DiFrancesco JC, Zedde M, et al. Spontaneous ARIA-like events in cerebral amyloid angiopathy-related inflammation: a multicenter prospective longitudinal cohort study. Neurology. 2021;97(18):e1809-e1822. https://doi.org/10.1212/WNL.0000000000012778
- 3- Regenhardt RW, Thon JM, Das AS, et al. Association between immunosuppressive treatment and outcomes of cerebral amyloid angiopathy–related inflammation. JAMA Neurol. 2020;77(10):1261-1269. https://doi.org/10.1001/jamaneurol.2020.1782
- 4- Bridel C, Hoffmann T, Meyer A, et al. Glutaminyl cyclase activity correlates with levels of Aβ peptides and mediators of angiogenesis in cerebrospinal fluid of Alzheimer's disease patients. Alzheimers Res Ther. 2017;9(1):38. https://doi.org/10.1186/s13195-017-0266-6
- 5- Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimers Dement. 2023;19(2):658-670. https://doi.org/10.1002/alz.12694
- 6- Rashad A, Rasool A, Shaheryar M, Sarfraz A, Sarfraz Z, Robles-Velasco K, Cherrez-Ojeda I. Donanemab for Alzheimer's Disease: A Systematic Review of Clinical Trials. Healthcare (Basel). 2022 Dec 22;11(1):32. doi: 10.3390/healthcare11010032. PMID: 36611492; PMCID: PMC9818878.
- 7- Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM; TRAILBLAZER-ALZ 2 Investigators. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023 Aug 8;330(6):512-527. doi: 10.1001/jama.2023.13239. PMID: 37459141; PMCID: PMC10352931.


Thank
you