Alzheimer’s disease

An international perspective

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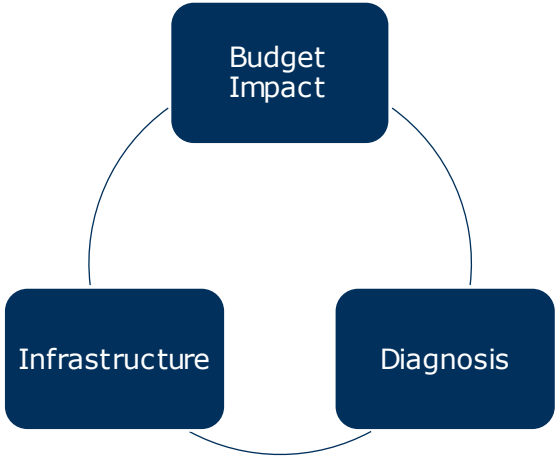
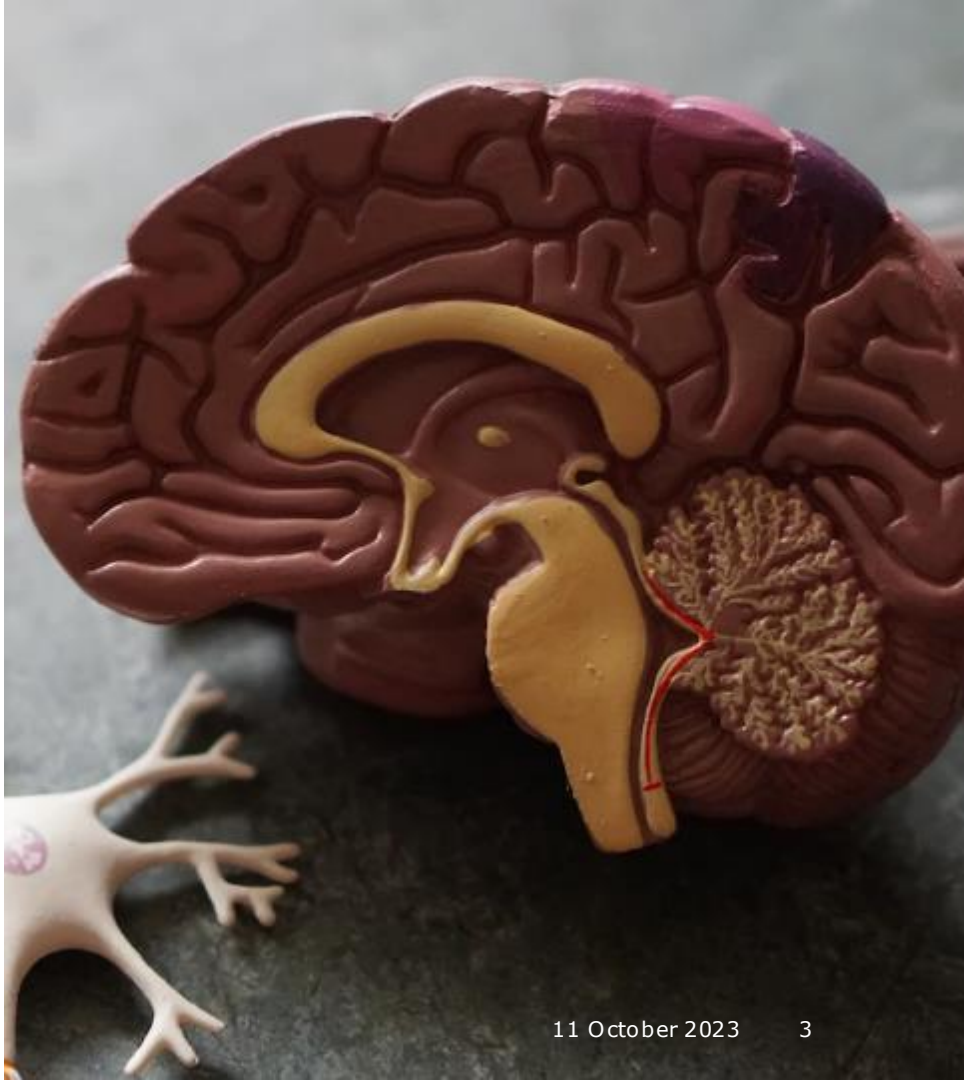
Contents

Key Questions

- *Are we better off investing in research than spending it on medicines of which we do not know if they work?*
- *Are we ready to treat thousands of patients with Alzheimer's disease?*





Impact on budget

- Estimates of the number of patients eligible for treatment with lecanemab, for prodromal / mild ADs in Europe is estimated to be at least 5 million*
- The price of lecanemab in the US for a year treatment is $ 26.500
- If all patients were treated this would amount to over $ 130 billion in one year
- This is only the drug, not taking into account the cost of diagnosis, continuous monitoring and other care required

$ 130 billion per year in EU

**EASD Lancet 2023*

Diagnosis

- Drugs targeting amyloid removal from the brain currently require patients to be diagnosed using neuroimaging (MR and PET) of taking a sample of the cerebrospinal fluid (CFS) or potentially through the use of plasma biomarkers
- Neuro-imaging and CFS are costly and timely procedures
- The amount of patients to be tested is likely higher than the patients eligible for treatment
- How are patients found who have 'mild' symptoms?
- The use of plasma biomarkers could be promising but needs further research before it can be used widely

5 million patients?

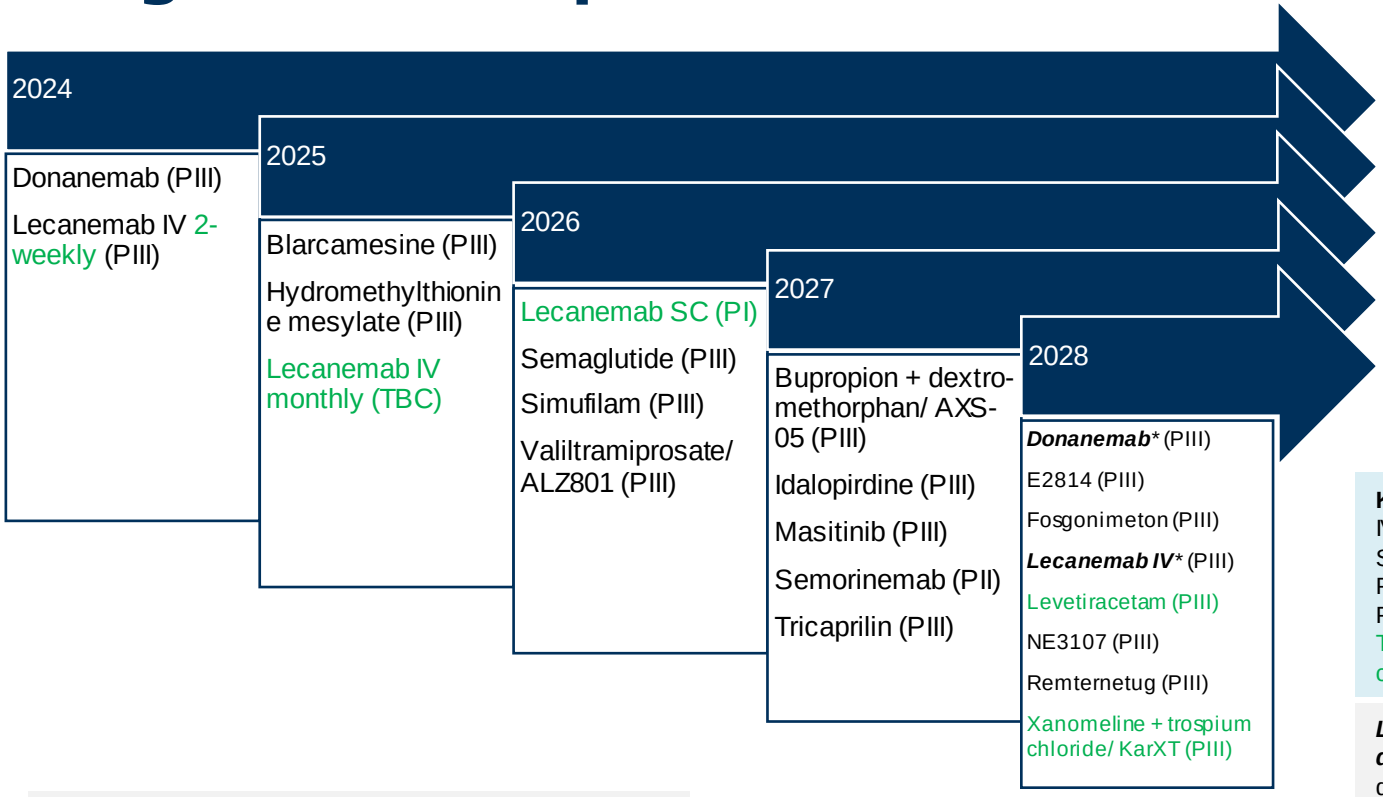
Infrastructure

- While on treatment patients require continuous monitoring including neuroimaging
- This requires a facility that can perform diagnosis and provide the necessary follow up for this type of treatment
- It would require huge capacity from such centres to be able to deal with all the patients

How many doctors and nurses?

What is coming?

Drugs in development 2023 – 2028



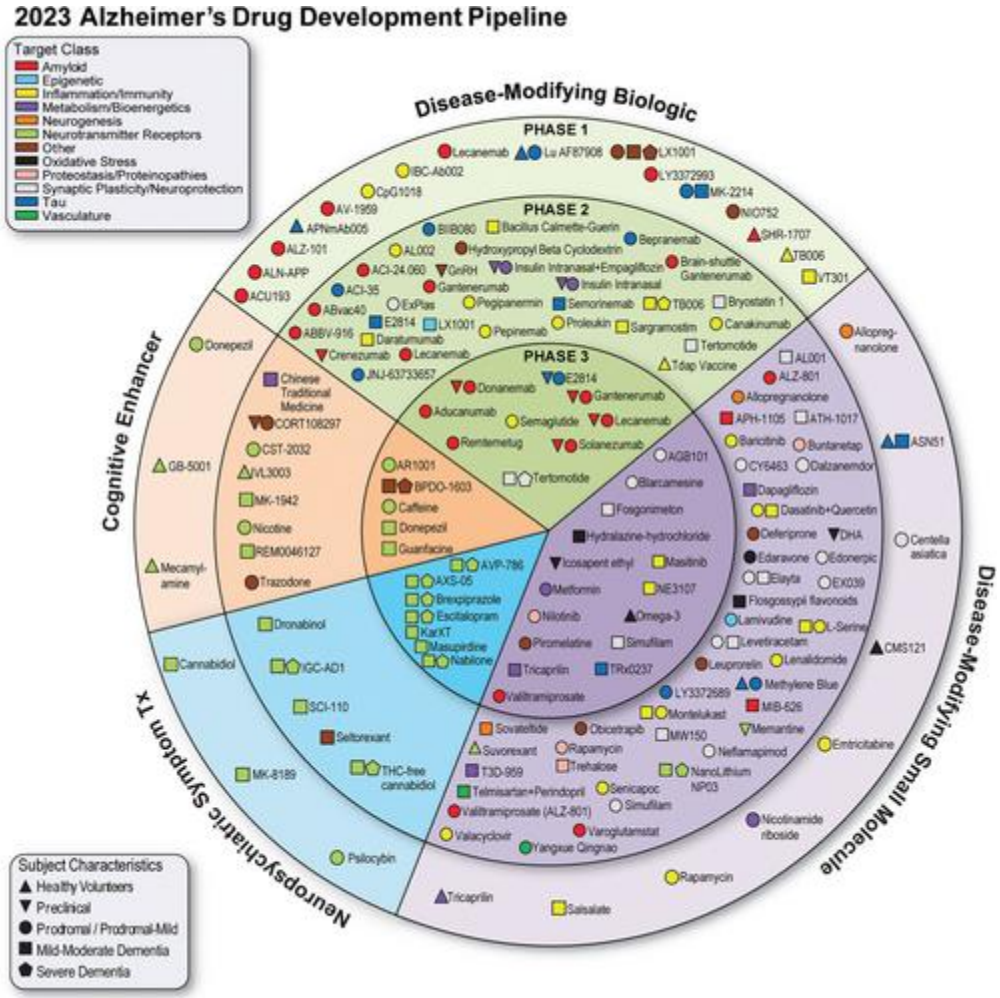
KEY
IV intravenous
SC subcutaneous
PII Phase 2 clinical trial
PIII Phase 3 clinical trial
TBC Trial phase to be confirmed

Lecanemab IV and ***donanemab*** are in development for early Alzheimer's disease (due 2024) and pre-clinical Alzheimer's disease* (due 2028)

Please note: Launch plans are estimates (based on publicly available information) and are subject to change

AD Pipeline is Diverse

- 187 PHI, II and II trials assessing 141 unique medicines
- 36 in PHIII
- 87 PHII
- 31 PHI

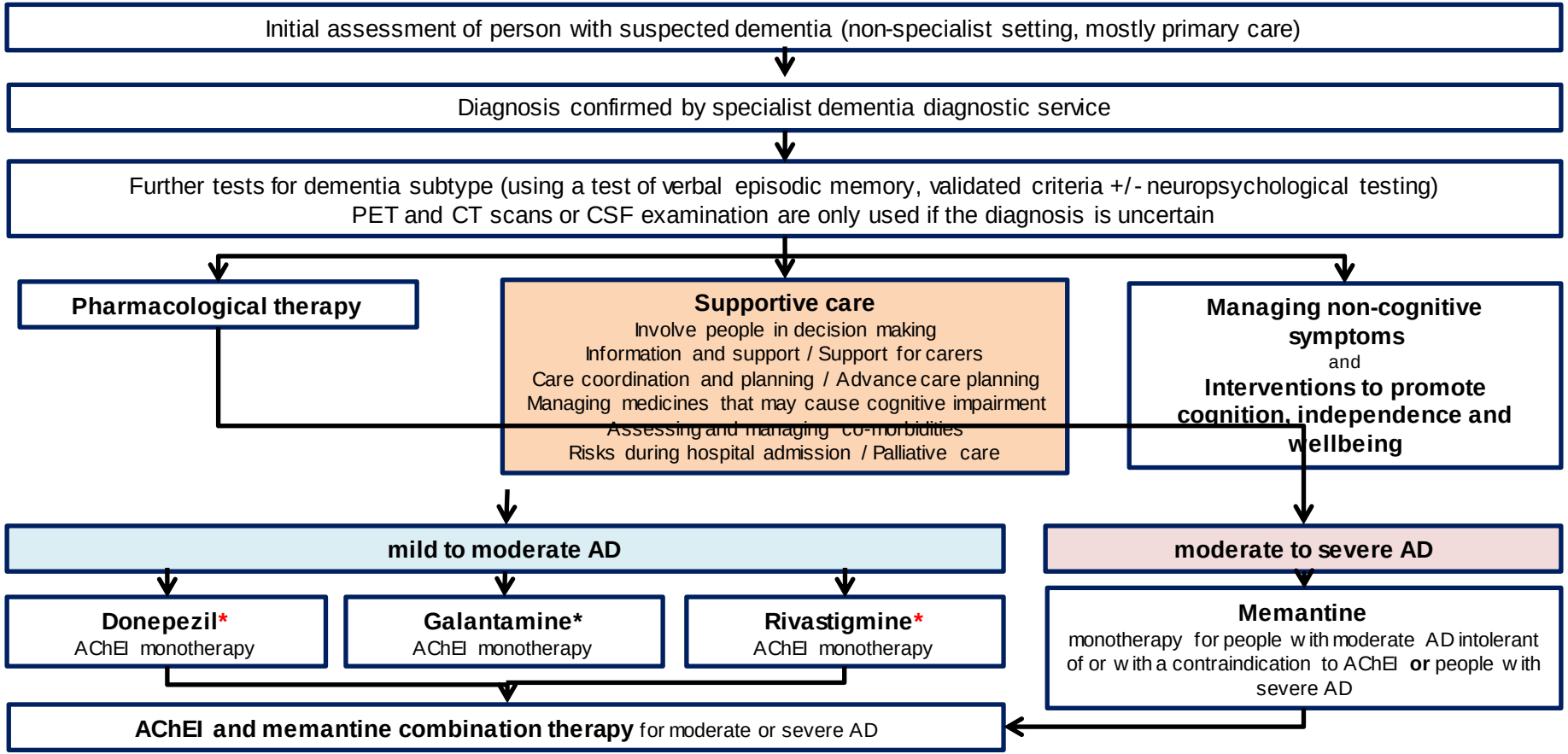


Source: Cummings 2023 Alzheimer's & Dementia: Translational Research & Clinical Interventions

Failure rate in AD remains high

Generic Name	Company UK	Indication	Additional Details	Route
atuzaginstat	Cortexyme	Alzheimer's disease	mild-to-moderate (MMSE 12-24)	Oral
azeliragon	vTv Therapeutics	Alzheimer's disease	mild, in patients with type 2 diabetes	Oral
elenbecestat	Biogen - Eisai	Alzheimer's disease	early stage	Oral
gantenerumab	Roche	Alzheimer's disease	early (MCI and mild)	Subcutaneous injection
lanabecestat	AstraZeneca	Alzheimer's disease	early-stage	Oral
nilvadipine	Archer Pharma-ceuticals	Alzheimer's disease	mild-to-moderate - first or second-line	Oral
solanezumab	Eli Lilly	Alzheimer's disease	mild to moderate, to delay disability	Intra-venous infusion
solanezumab	Eli Lilly	Alzheimer's disease	in patients pre-AD with brain amyloid pathology (early-stage)	Intra-venous infusion
troriluzole	Biohaven Pharma-ceuticals	Alzheimer's disease		Oral
umibecestat	Amgen	Alzheimer's disease		Oral
verubecestat	Merck Sharp & Dohme (MSD)	Alzheimer's disease	mild to moderate	Oral
verubecestat	Merck Sharp & Dohme (MSD)	Alzheimer's disease	prodromal (early-stage)	Oral

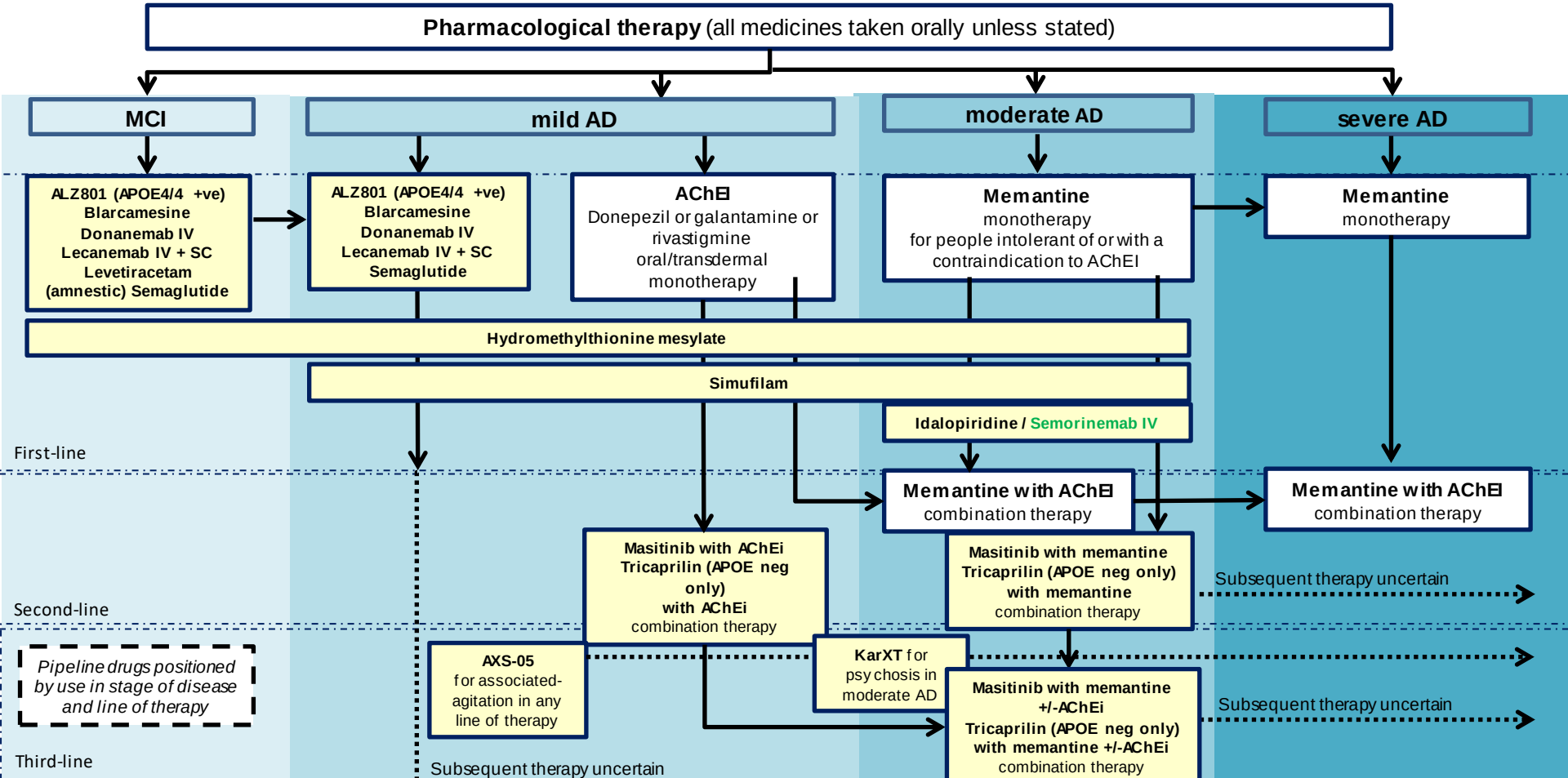
Alzheimer's disease (AD) – Current pathway



*Patients can switch between these

www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/dementia

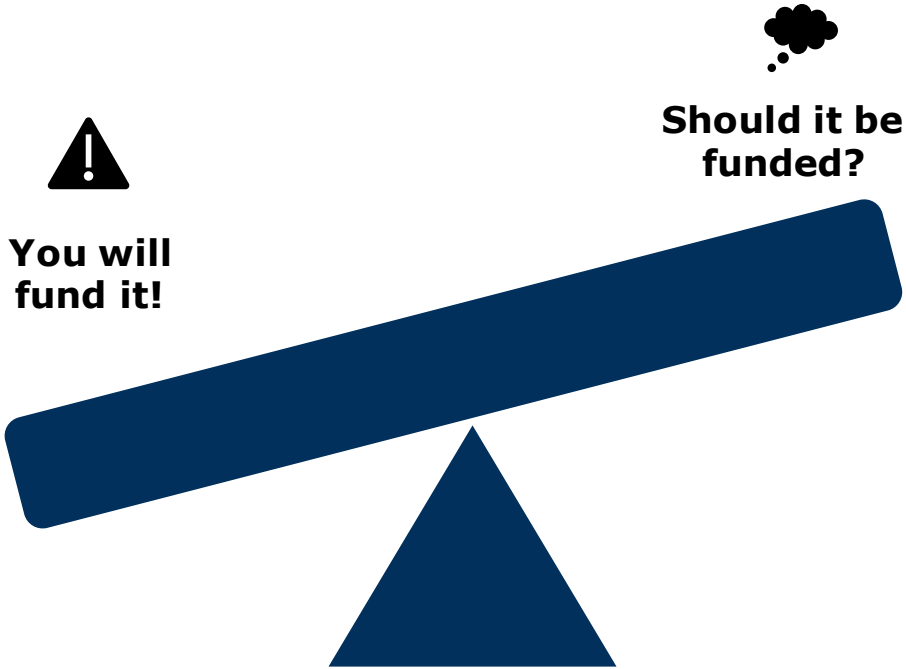
Phase 3 drugs for Alzheimer's disease (AD) due 2023 to 2027 – Proposed pathway



Payer perspective

- UK – NHS Commissioning
- NL – Ministry of Health
- Beneluxa Initiative

Can you have a rational scientific discussion within such an emotionally charged therapy area?



What can we learn from the past? Example from MS

Beta interferons

Scientific knowledge increases

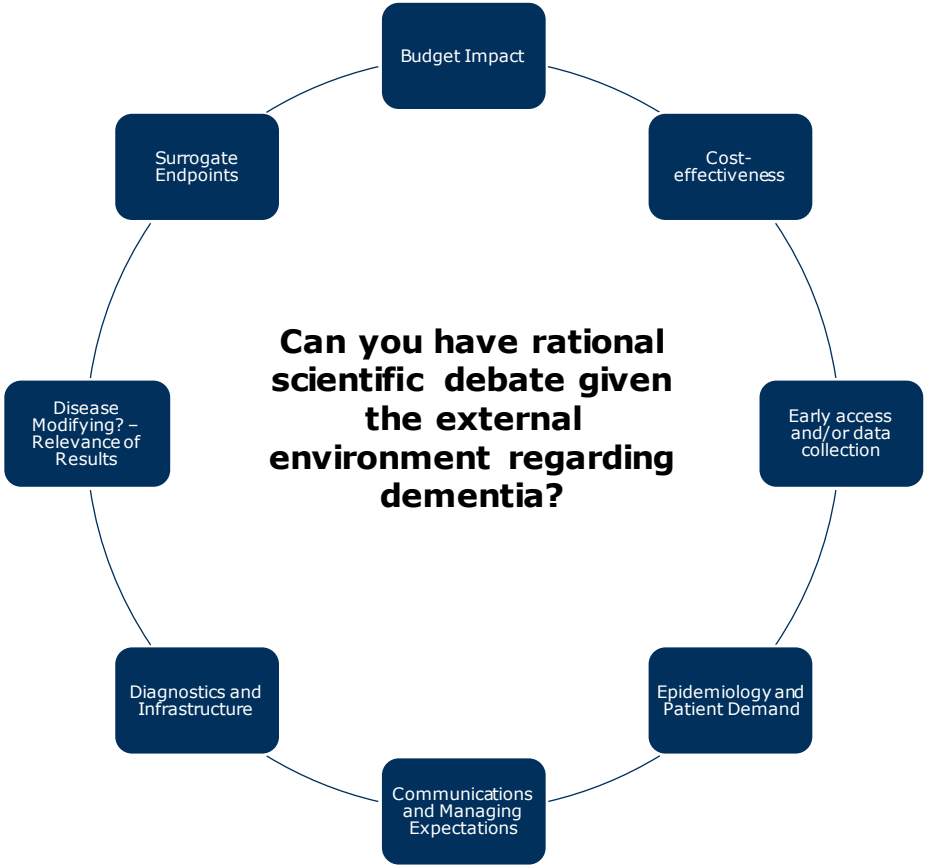
Pharmacological targets and development increases

Care pathway is more dynamic

Future therapies (e.g., ocrelizumab, Siponimod, teriflunomide)

- ✓ Disease Modifying Therapies (DMTs)
- ✓ Modest benefit in population with very high unmet need
- ✓ Political pressure to fund
- ✓ Platform for future therapies
- ✓ Set pricing benchmark

Summary of Payer Issues



Anti amyloids – donanemab & lecanumab

Donanemab

- Product: Donanemab
- Indication: Alzheimer's disease
- Manufacturer: Eli Lilly
- Mechanism of action: anti-amyloid
- Expected registration (EMA): 2023
- Trial design(s): PHIII RCT against placebo (TRAILBLAZER)
- Other:
  - Acquisition of:
    - Prevail, amongst several therapies for Parkinsons and Dementia – for 750 million
  - Lilly also is studying: Remternetug PHII AD, Gene therapy Parkinsons PHII, PHII – O-glcnacase INH – AD, Gene therapy Dementia
  - R&D spent approx. 1/3 – ¼ of company's revenues – in 2022, 7 billion in RD, projected 8 billion in 2023
  - Line extensions to be expected (earlier ADs)

Lecanumab (Leqembi)

- Product: Lecanumab
- Indication: Alzheimer's disease
- Manufacturer: Biogen and Eisai
- Mechanism of action: anti-amyloid
- Expected registration (EMA): end 2023
- Trial design(s): PHIII RCT (Clarity)
- Other:
  - Product a collaboration between Biogen and Eisai – share of all losses and profits
  - Company also filing approval for a SC version
  - In the US, the companies estimated the product to be worth $ 37.600, but instead lowered to price to $ 26500 – claiming that in doing so they generate savings
  - Forecasts expect billions of revenues over the next years, with over $ 4 billion to be expected in the year 2028
  - Line extensions to be expected (earlier ADs)

Clinical uncertainty

Impact on willingness to pay

- For the pharmaceuticals that target the Amyloid beta accumulation:
  - It is not yet established whether there actually is a correlation between the reduction in amyloid beta and cognitive benefit
  - Safety risks – cerebral oedema in particular - of these anti amyloids are an issue and are perhaps snowed under by the hope of patients that these drugs may have an effect
  - Studies seems to focus on the slowing of the decline – but there is still a decline with these drugs
    - What is a clinically significant less rate of decline?
  - Critique on trial design and the in and exclusion criteria of patients, as well as the drop-out rate
  - The use of the scores to determine the effect size seems impervious
  - Are the right patients targeted and will not simply everyone put on treatment?

$ 130 billion for uncertainty?

Uncertainty about cost-effectiveness

Impact on willingness to pay

- For the pharmaceuticals that target the Amyloid beta accumulation:
  - Clinical uncertainties will be reflected in the cost effectiveness ratio
  - With such large expenditure are we willing to accept any risk on such a therapy not being cost-effective
  - There are other costs that could be taken into account, since the drug is only a part of the picture
- donanemab may not be CE (JAMA 2022 (Ross et al.))

$ 130 billion for uncertainty?

Cost base arguments?

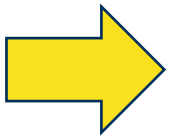
Impact on willingness to pay

- Much public research has gone into treatments for ADs, but also on many other areas relating to treating patients with ADs
- Companies are likely to use the argument of cost of failure of research into ADs – a study commissioned by Biogen points out that so far over $ 40 billion has been invested in studies, however almost none of it has come to fruition
- What is fair?

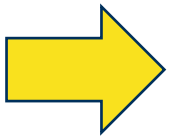
$ 130 billion for shareholders?

Key Points

1. Dementia remains a key political priority across health systems with a high media profile – this emotional environment, makes rational and scientific discussion challenging
2. The first generation of these products have limited efficacy with strong side-effects – but in an area of high unmet need
3. The scale of the budget impact is not limited to just the pharmaceuticals – the infrastructure and service preparedness are core elements as well



Given the scenario – is the investment a good use of public resources?



How do we collaborate and share experience and expertise to facilitate optimal negotiations and realistic entry of these products?

Questions?