Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

For committee – confidential information redacted ([redacted])

Third appraisal committee meeting

Technology appraisal committee D [14 May 2025]

Chair: Dr Megan John

External assessment group: Kleijnen Systematic Reviews Ltd

Technical team: Owen Swales, Lizzie Walker, Ross Dent

Company: Eisai Ltd

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease

- ✓ **Background and ACM1 recap**
- ❑ Consultation responses (excluding company)
- ❑ Company response and key issues
- ❑ Cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

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Lecanemab (Leqembi, Eisai)

Marketing authorisation MHRA	• August 2024 • For treating 'mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε4 (APOE-4) heterozygotes or non-carriers'
Mechanism of action	• Accumulation of amyloid-beta (Aβ) plaques + tau tangles characterise Alzheimer's disease (AD) • Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against Aβ marking it for immune system to clear • May reduce levels of tau, another biomarker of AD, in the brain
Testing prior to treatment	• Must confirm Aβ by PET or CSF • Should test for APOE-4 status
Administration	• Recommended dose 10 mg/kg, as a 1-hour IV infusion every 2 weeks • Discontinue lecanemab once patient progresses to moderate AD
Price	• List price: £275.00 for 200 mg solution for infusion; £545.00 for 500 mg solution • Average monthly cost [redacted] (based on Clarity AD trial European patients) • Updated patient access scheme discount for committee meeting 3

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; APOE-4, apolipoprotein E ε4; CSF, cerebrospinal fluid; MHRA – Medicine Healthcare product Regulatory Agency; PET, positron emission tomography

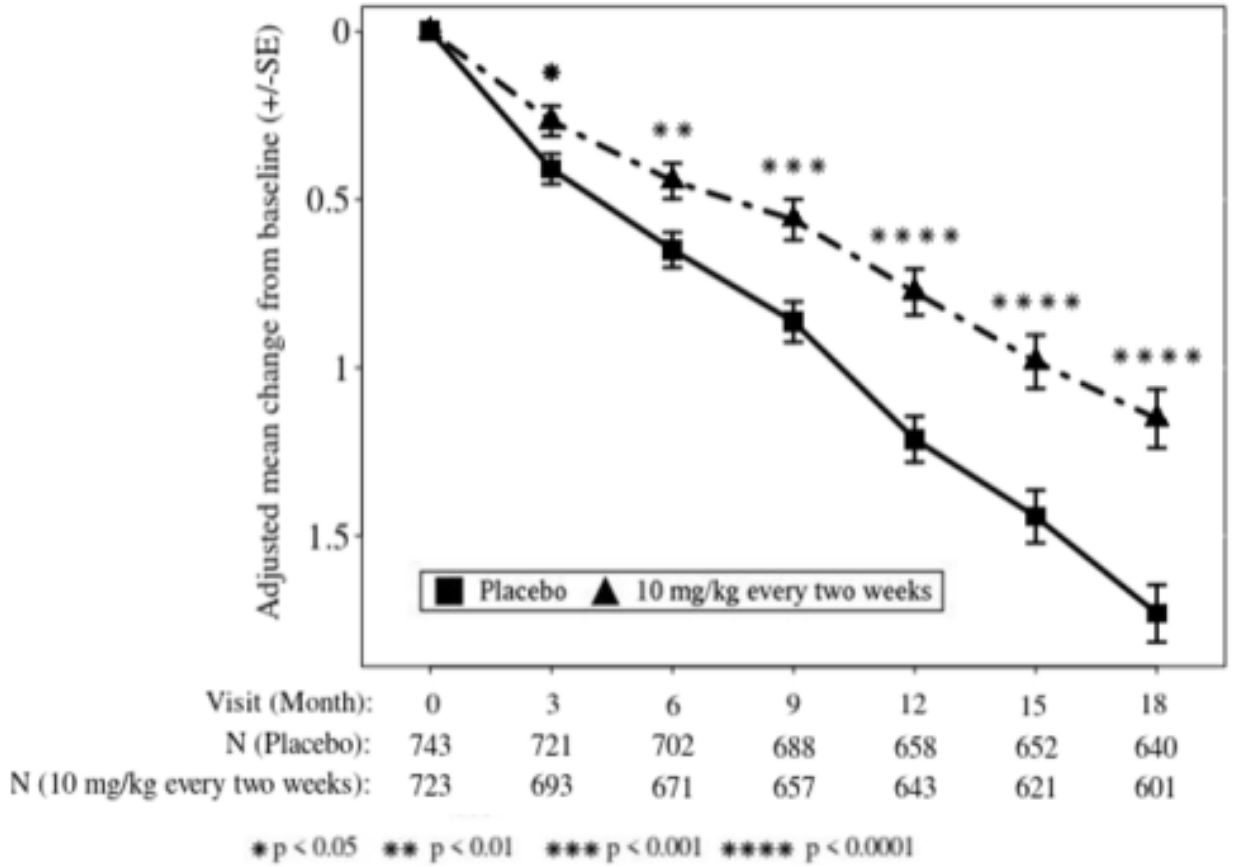
Key clinical trial

Lecanemab reduces decline in CDR-SB by 33% at 18 months vs placebo

Features of the Clarity AD trial

Design	Phase 3, multicentre, randomised, double-blind
Population	Adults with early AD
Intervention	Lecanemab
Comparator	Placebo
Duration	18 months with ongoing open label extension
Primary outcome	Change in CDR-SB at 18 months
Secondary outcomes	Change in amyloid PET, ADAS-Cog, ADCOMS, ADCS MCI-ADL at 18 months
Locations	Global including 8 UK sites
In model?	Yes

Adjusted mean change from baseline in CDR-SB in Clarity AD for the indicated population



Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADCOMS, Alzheimer's disease composite score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; PET, positron emission tomography

Committee conclusions at 2nd committee meeting (ACM2)

Lecanemab is not recommended for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease in adults who are apolipoprotein E4 heterozygotes or non-carriers

Summary of committee conclusion:

- Committee recalled the significant unmet need for treatment options and high uncertainty associated with the face validity of the company's model and long-term evidence
- All cost-effectiveness estimates were above the range normally considered a cost-effective use of NHS resources
- The modest benefit to patients demonstrated in the trial, balanced with the decision-risk associated with the substantial resources the NHS would need to commit to implement access to lecanemab would be too great
- Managed access not suitable due to lack of plausible cost effectiveness and concerns that additional data collection would not resolve the uncertainties
- Did not recommend lecanemab either for routine NHS use or with managed access

Consultation responses received from:

Company (Eisai), Association of British Neurologists, Alzheimer's Research UK, Alzheimer's Society, UK Clinical Pharmacy Association, Royal College of Psychiatrists, UCL Dementia Research Centre, Web comments (n=3)

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Abbreviations: ACM, appraisal committee meeting; UCL, University College London

Committee preferences and uncertainties at ACM2

Committee preferred assumptions

- See full list in appendix
- Company have incorporated some of the committee preferences at ACM2 in its updated submission

Committee identified uncertainties

- Proportion of people who move directly from mild to severe dementia with lecanemab
- Impact of treatment discontinuation on outcomes
  - **Committee:** appropriate to include some treatment waning that is based on evidence
- How the stopping rule for lecanemab would be applied in practice, and the impact on costs
  - **Committee:** uncertain if necessary to include quarterly outpatient appointments?
- Difference in carer utility values between community and residential care
  - **Committee:** uncertain if necessary to include 0.09 carer disutility on entering residential care?
- Infusion costs
  - **Committee:** uncertain if company's micro-costing estimate or cost for coronavirus monoclonal antibodies shared by NHS England more appropriate?

Abbreviations: ACM, appraisal committee meeting

Key issues to discuss

Key issue	Company approach for discussion	ICER impact
Progression from mild to severe AD	• Company: Lecanemab reduces proportion of people who move directly from mild to severe AD. EAG: no treatment effect of lecanemab on this	Medium
Stopping rules	• Committee at ACM2: Not appropriate to apply stopping rule on entry to residential care → company continues to apply • Company: Implementation of stopping rule on progression to moderate AD will not require additional resources	Medium
Treatment waning	• Company: Includes new treatment effect waning assumptions linked to amyloid plaque re-accumulation	Medium
Infusion costs	• Company: Still includes infusion cost based on micro-costing study	Large
APOE4 testing costs	• Company: Uses Scottish Health Service value, rather than NHSE value	Small
Carer utility values	• Company: Includes 1.8 carers, based on committee preference in donanemab appraisal • Argues carer utility values are still underestimated, explores in scenarios	Large

Abbreviations: ACM, appraisal committee meeting; AD, Alzheimer's Disease; APOE4, apolipoprotein E 4

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Summary of consultation responses

See detailed responses in appendix

Diagnostic tests and treatment pathway

- Will be a shift to earlier presentation as public awareness of treatments grows
- Blood test for AD pathology available in UK, could be used to rule out some people from further testing
- Lecanemab has moderate gains vs burden, so may be better to invest in novel pathways and overall care

Carer quality of life

- "True" carers' quality of life is not captured, most people starting treatment would have a minimum of 1 carer
- Survey results (n=254): mean QoL rating having a partner with mild dementia: 0.58, with severe dementia: 0.27

Stopping rule

- Progression should be monitored with routine follow-up
- Look at 18-month stopping rule to align with donanemab and Clarity AD

Severity modifier (appendix)

Concern that not eligible for severity modifier given disease burden

Infusion costs

- 3 experts estimated infusion costs to be £250 to < £500
- Significant burden for infusion units already at full capacity

Managed access

- Support for managed access, RWE needed
- Managed access data burden too great

Lecanemab treatment effect

- Cause of AD is uncertain so progress will be stepwise and modest, also trials lack diversity
- Marginal benefits do not outweigh costs, long-term treatment effect uncertain and below minimal clinical benefit

Abbreviations: AD, Alzheimer's Disease; QoL, quality of life; RWE, real world evidence

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Changes to the company base case for ACM3

Assumption	Company base case	Company rationale
Population	Baseline distribution of patients across MCI and mild AD states (20.4%:79.6%) [donanemab TRAILBLAZER trial]	To align with committee preferences at ID6222 (donanemab) ACM2
Caregivers	1.8 caregivers per patient (GERAS study) [see slide]	
Private health care costs	Health state costs from Wittenberg et al. 2019	
Mortality	General population mortality for MCI (HR=1)	Committee preference at ID4043 ACM2
Treatment waning	Treatment waning for all off-treatment health states using mean PET levels from Clarity AD and amyloid re-accumulation rates [see slide]	
Utility values	Patient-reported EQ-5D (using a MMRM) for MCI and mild dementia health states [see slide]	
APOE-4 testing costs	Scottish APOE4 testing costs (£41.10) [see slide]	No verifiable costs in England

Is it appropriate for the above changes in yellow to be made to align ID4043 and ID6222?

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Abbreviations: ACM, appraisal committee meeting; AD, Alzheimer's disease; APOE-4, apolipoprotein E 4; HR, hazard ratio; MCI, mild cognitive impairment; MMRM, mixed model with repeated measures; PET, positron emission tomography

ICER impact: approx. +£3k

Key Issue: Progression from mild to severe AD

Uncertain if lecanemab affects progression directly from mild to severe AD

Committee at ACM2

- Uncertain whether having lecanemab would affect the proportion of people who progressed directly from mild to severe dementia (EAG base case assumed having lecanemab would not affect the proportion)

Company

- Not appropriate for the time-to-worsening hazard ratio for mild to severe AD to be disabled, as this decreases the overall treatment effect of lecanemab so it is not reflecting the efficacy observed in Clarity AD
- In Clarity AD, a treatment effect on the transition from mild to severe AD is observed, as [redacted] patients in the placebo arm (n= 743) transitioned from mild to severe in contrast to [redacted] patients in the lecanemab arm (n=723)

EAG comments

- No evidence of significant treatment effect in transition from mild to severe dementia
- Company's model under-estimates relative state occupancy in severe AD of lecanemab vs SoC compared with observed state occupancy in Clarity AD
- So, EAG disables relative treatment effect for the transition from mild to severe AD in its base case

Abbreviations: ACM, appraisal committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; SoC, standard of care

Would lecanemab affect the proportion of people who progress from mild to severe dementia?

ICER impact: approx. +£2.5k

Key Issue: Stopping rule for residential care

Company maintains residential care stopping rule in base case

Committee at ACM2

- Not appropriate to apply a lecanemab stopping rule based on entry to residential care because there is inequitable access to residential care, so this could lead to increasing health inequalities

Company

- Residential care stopping rule is not a formal stopping rule, but a reflection of what happens in clinical practice
- 2 experts said continuing treatment in residential care "would not be appropriate" and "bad practice"
- Rate of admissions for residential care used in model (Knapp et al. 2016) reflects those requiring permanent, not temporary or respite care
- Clinical expert opinion estimated the number of people entering residential care permanently with mild AD would be extremely small (approx. 5-10%) which is in line with the model ([redacted]% of life years in residential care)
- Base case stops treatment on entering residential care; scenario with 10% of people still on treatment

EAG comments

- Details of expert validation of residential stopping rule not provided, question whether experts knew the exact context was people with mild AD entering permanent residential care (which is approx. [redacted]% of people in model)
- Note possible logistical challenges for continuing care, so base case assumes arbitrary 50% continue treatment
- Share scenario with committee preference from ACM2 (100% with mild AD remain on treatment in care)

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Abbreviations: ACM, appraisal committee meeting; AD, Alzheimer's disease

Would people with MCI or mild AD have lecanemab in residential care?

ICER impact: approx. +£1k

Key Issue: Stopping rule for disease progression

Committee was uncertain on the resource impact of a progression stopping rule

Committee at ACM2

- Uncertain if company's or EAG's model captured the resource impact of the disease-progression stopping rule

Company

- No additional resource required as functional assessments could be carried out during routine infusion visits
- But share scenario with 6-monthly outpatient visits to reflect uncertainty and some expert opinion

Stakeholders

- Stopping rule should be easy to implement as treatment follow-up will be carried out anyway
- Appropriate resourcing needed as infusion burden alone will exceed current capacity of units

EAG comments

- Functional tests likely require more or different staff time than infusion visit monitoring, but this is uncertain
- Monitoring necessary for treatment decisions so should be included, unclear whether 3- or 6-monthly outpatient visits are appropriate, but include 6-monthly visits as EAG base case includes higher NHSE infusion costs
- Model allows people to transition to moderate AD and discontinue in same cycle, likely underestimates costs

Abbreviations: ACM, appraisal committee meeting; AD, Alzheimer's disease

Would progression be monitored at routine infusion visits, or additional monitoring needed?

ICER impact: approx. +£2k

Key Issue: Treatment effect waning (1)

Company uses new approach based on amyloid re-accumulation rates

Committee at ACM2

- Inappropriate to assume people who stop treatment have the same benefits as people on treatment or lose benefits immediately and completely, scenarios exploring this must be based on robust clinical expectations

Company

- Clinical experts: treatment effect maintained while amyloid plaque levels are within amyloid negative range
- Updated base case: treatment waning applied to all discontinued patients, regardless of discontinuation reason and waning increases linearly to 100% at the end of a timepoint aligned with amyloid re-accumulation rate
- Waning starts when amyloid level is 30CL (amyloid negative threshold) and no treatment effect when amyloid levels are 50CL, amyloid re-accumulation rate is 2.6CL per year (Study 201) [aligned with ID6222 donanemab]
- [redacted]
- [redacted]

EAG comments: Company approach is uncertain because:

1) Assumption that treatment effect is directly linked to amyloid clearance is unclear
2) Quoted amyloid re-accumulation rate is from very limited study follow-up, likely underestimated
3) In model, treatment effect lost [redacted] years after stopping treatment, [redacted] have full treatment effect at 16 years

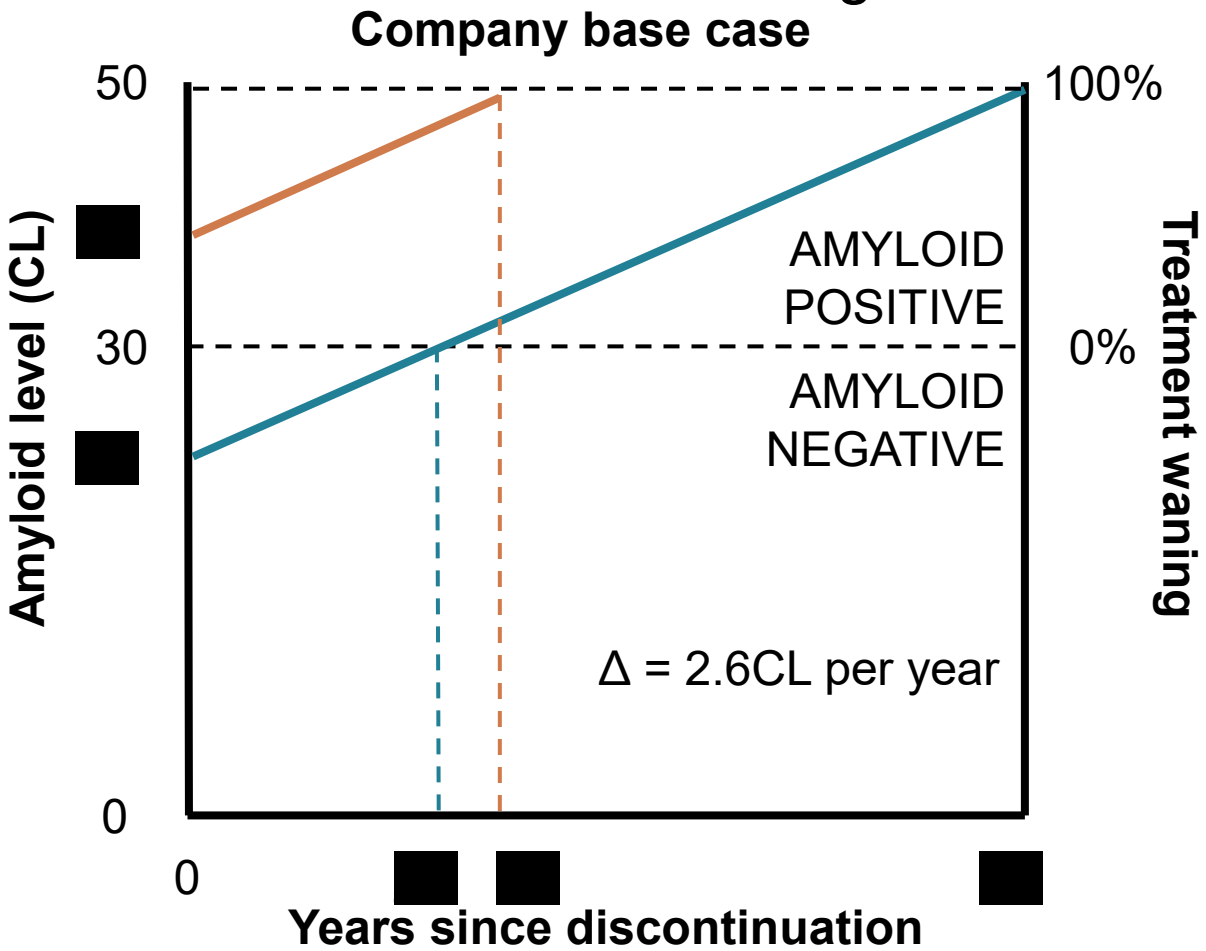
Base case: pre-18-months, immediate treatment effect waning with 4-year duration; post-18 months, 1 year until start of treatment waning (in line with donanemab) and 4-year treatment waning (considers optimistic)

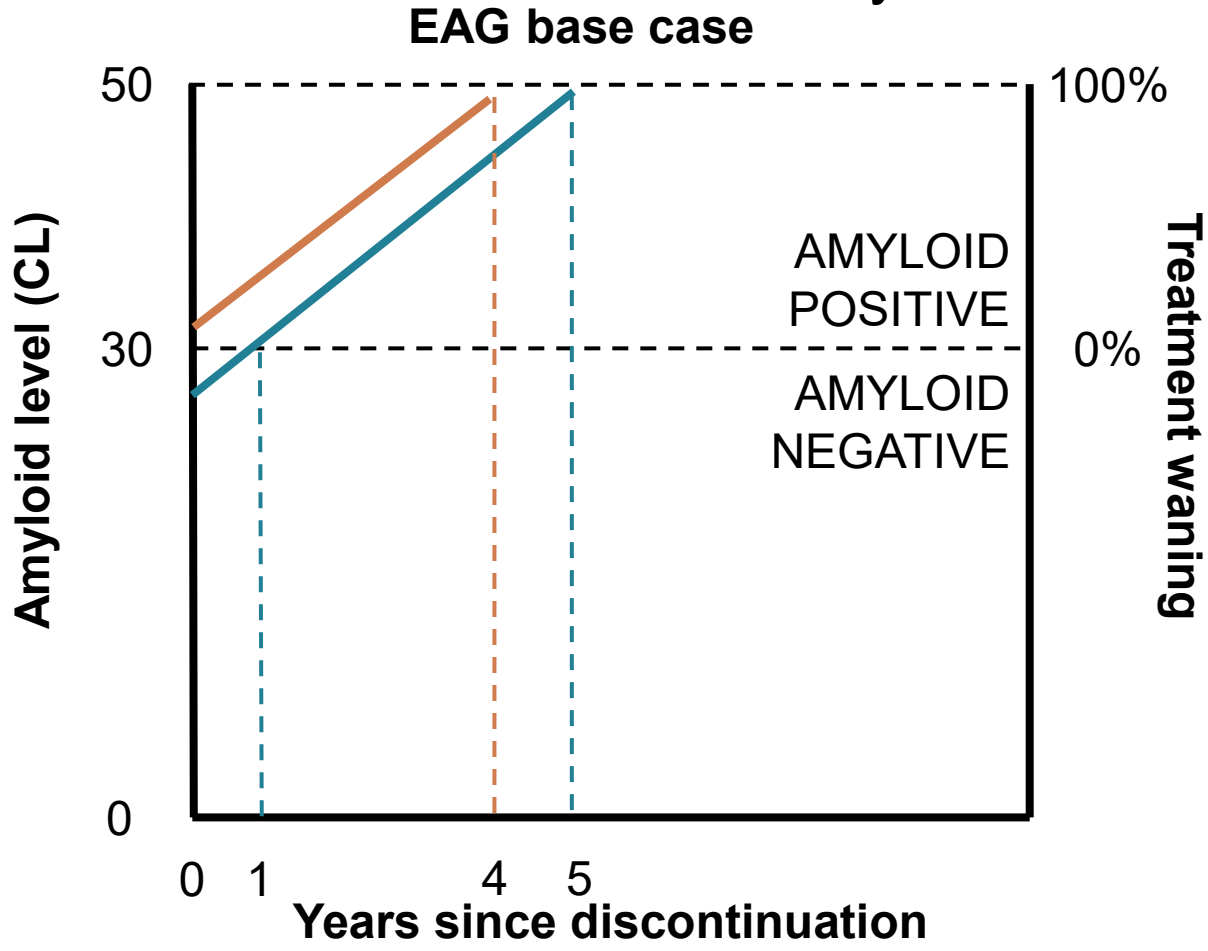
 Abbreviations: ACM, appraisal committee meeting; CL, centiloids

ICER impact: approx. +£2k

Key Issue: Treatment effect waning (2)

EAG links treatment waning to time since discontinuation rather than amyloid levels





When discontinuing before 18 months

When discontinuing after 18 months

EAG: do not follow company approach of basing treatment waning to amyloid levels, waning instead based on time since discontinuation

NICE Abbreviations: CL, centiloids

How should treatment effect waning be included in the model?

ICER impact: approx. +£22k

Key Issue: Infusion costs (1)

Company: £139 (micro-costing), NHSE: £432 (COVID monoclonal antibodies)

Committee at ACM2: Unable to determine a preference, appropriate cost likely closer to the NHSE estimate

Company (note: previously preferred cost of £207.59, code SB12Z for chemotherapy infusion)

- Base case unchanged, uses micro-costing infusion cost accounting for 30.8 minutes HCP time (£139.12)
- Shares scenario with increased cost to include overhead costs for full 60 minutes infusion (£149.26)
- Using highest estimated value for each component of micro-costing infusion cost still only yields £203.16
- Micro-costing includes PSSRU unit costs for overheads and capital overheads, weighted for shared use of space
- NHSE preferred cost is inappropriate as it includes costs required for establishing COVID Medicines Delivery Units which are temporary facilities, these satellite service set-up costs should not be attributed to lecanemab
- NHSE has also applied a Market Forces Factor and has not provided a transparent break down of included costs

Alzheimer's Research UK: 3 clinicians estimated lecanemab infusion costs to be £250 to < £500

NHSE: see next slide

EAG comments

- NHSE estimate may be high, but infusion-related reactions, some patients' complex needs and health state assessments are not incorporated in the chemotherapy infusion cost nor the company's micro-costing
- Base case uses NHSE estimate but only 6-monthly (not 3-monthly) outpatient visits, further info might be helpful

Abbreviations: ACM, appraisal committee meeting; HCP, health care practitioner; PSSRU, Personal Social Services Research Unit

How should infusion costs be included in the model?

ICER impact: approx. +£22k

Key Issue: Infusion costs (2)

NHSE preferred £432 estimate is at lower end of estimates for infusion cost

NHS England

- Currently no HRG code that covers a monoclonal antibody infusion to treat AD → likely available in 3 years
- In interim, normal to agree a price to be paid to NHS providers using an estimate based on similar activity
- Average price for an infusion of a monoclonal antibody in AD was calculated based on number of episodes of intravenous infusion with monoclonal antibodies from the NHSE secondary use service dataset
  - See appendix for detailed database search
- Result is an estimated cost of £361 for 2021/22 which is adjusted as follows:
  - 10% COVID uplift factor (pricing team advise resource for this type of infusion similar to COVID): £397
  - Inflation to 2024/5 prices: £434
  - Market forces factor applied: £462
- Estimated cost from 2023/24 inflated to 2024/25 prices: £489
- Also, removing a data restriction for specifying monoclonal antibodies in the coded data increases cost to £589
- Prefer to use £432 for infusion costs (based on older inflation figures available at time of NHSE submission) but note this is at the lower end of estimates for infusion costs

How should infusion costs be included in the model?

Abbreviations: AD, Alzheimer's disease; HRG, healthcare resource group

ICER impact: approx. +£0.5k

Key Issue: APOE4 testing costs

Company has challenged the unit testing costs in modelling

Committee at ACM2:

- Not discussed in previous ACMs

Company

- Unable to verify APOE4 unit testing cost ([redacted]) used previously from NHSE budget impact submission, so use a cost from the Scottish Health Service that can be verified (£41.10, R130 Laboratory Services, Clinical Genetics)

APOE4 testing costs breakdown	Previous base case	ACM3 base case
Unit testing cost (changed for ACM3)	[redacted]	£41.10
Outpatient appointment (unchanged)	[redacted]	[redacted]
Genetic counselling, weighted by uptake (unchanged)	[redacted]	[redacted]
Total testing costs	[redacted]	[redacted]

EAG comments

- Considers Scottish cost to be relevant and includes this in its base case
- Also explores a scenario that uses the NHSE estimate

Abbreviations: ACM, appraisal committee meeting; APOE4, apolipoprotein E 4

What value should be used for APOE4 testing costs? [redacted] or £41.10?

ICER impact: approx. +£4.5k

Key Issue: Carer utility values

See more detail in appendix

Company argues EQ-5D underestimates carer utility, explores in scenario

Committee at ACM2

- Incremental approach to carer QALYs was reasonable and preferred to use it for decision making
- Uncertainty with utility difference in community and residential care and incremental approach for carer utility

Company

- Reed et al. (2017) shows EQ-5D underestimates AD carer QoL by comparing to Zarit Burden Interview (ZBI) tool
  - At 18 months, ZBI showed statistically significant 38.5% lower decline for caregivers of lecanemab patients vs placebo, whereas EQ-5D showed only approx. 10% mean difference vs placebo
- So, company did scenario analysis using company assumptions from ID6222 donanemab:
  - Utility difference between MCI and other states from vignette study applied to MCI caregiver utility from Clarity AD, with spouse / child caregiver utility in community setting weighted by 1.8 caregivers
- Company assumes additional disutility for carers of people in residential care (includes scenario removing this)

EAG comments

- Impact on QoL may be under-estimated when using EQ-5D and only 1 caregiver due to lack of sensitivity
- Committee in ID6222 preferred utility values from GERAS study over the vignette study (and 1.8 caregivers)
- EAG base case uses 1.8 carers, excludes residential care decrement due to potential overestimation
- Company scenario not in line with NICE reference case, may overestimate impact on carer QoL

Abbreviations: ACM, appraisal committee; AD, Alzheimer's Disease; MCI, mild cognitive impairment; H; QoL, quality of life

What approach for utility should be used?

Differences in company and EAG base cases

Assumption	Company base case	EAG base case
Transition probabilities	Include treatment effect on the transition from mild to severe AD	Disable treatment effect on the transition from mild to severe AD
Private health care costs	Health state costs from Wittenberg et al. 2019	Unclear if unpaid care costs excluded, so use previous approach that adjusted Alzheimer's society costs by 47.2%
Infusion costs	Micro-costing infusion cost (£139.12)	NHS England estimate (£432)
Stopping rules	No additional resource for monitoring progression Stop treatment in residential care	6-monthly outpatient visits for monitoring progression 50% with mild AD in residential care remain on treatment
Treatment waning	Treatment waning based on amyloid re-accumulation rates	Treatment waning for pre-18 months group immediately, for post-18 months group after one year, with duration of 4 years
Carer utility	0.09 disutility for caregivers when patient in residential care	Disable additional caregiver disutility when patient moves to residential care

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group

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Cost-effectiveness results: revised company base case

Company updated base case is <£30,000 / QALY, down from c. £40,000 / QALY

Table: Previous company base case (deterministic, previous PAS price)

Technology	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,525

Table: Revised company base case (deterministic, updated PAS price)

Technology	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,706

Table: Revised company base case (probabilistic, updated PAS price)

Technology	Total		Incremental		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£29,908
Lecanemab	[redacted]	[redacted]			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care

Cost-effectiveness results: company scenarios

Table: Company scenario analyses (PAS price)

Scenario	Deterministic PAS ICER
Company base case	**£29,706**
1. Micro-costing lecanemab infusion cost with overheads for full chair time	£30,471
2. Inclusion of the chemotherapy SB12Z code for lecanemab infusion	£34,870
3. Treatment effect waning for all off-treatment states based on time to return to baseline amyloid PET level ([redacted])	£26,547
4. Assume [redacted] for all off-treatment moderate to severe AD patients, 75% effect for other off-treatment states (EAG preference)	£28,614
5. 10% remain on treatment following permanent move to residential care	£30,225
6. Include six-monthly outpatient appointments	£30,995
7. Use of patient-by-proxy EQ-5D utility values for MCI and mild AD	£29,383
8. ID6222 caregiver utility and removal of caregiver disutility on institution	£19,039
9. Scenario 8 plus scenario 1	£19,529
10. Scenario 8 plus scenario 2	£22,349
11. Removal of caregiver disutility on institution	£34,056
12. Inclusion of the NHSE APOE4 test unit cost	£30,013

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; CL, centiloids; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme; PET, positron emission tomography

Cost-effectiveness results: EAG base case

EAG base case is substantially higher than £20 - £30,000 / QALY

Table: EAG base case individual changes to company base case and combined (deterministic, PAS price)

	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	£29,706
Health state costs: use Alzheimer's UK research and remove 47.2% private care costs	[redacted]	[redacted]	£32,023
Infusion costs based on NHS England estimate	[redacted]	[redacted]	£51,797
6-monthly outpatient visits for monitoring	[redacted]	[redacted]	£30,995
Treatment effect waning for pre-18 months group immediately, for post-18 months group after one year, with duration of 4 years	[redacted]	[redacted]	£31,902
50% of patients with mild AD in permanent care remain on treatment	[redacted]	[redacted]	£32,301
Disable treatment effect on the transition from mild to severe AD	[redacted]	[redacted]	£32,855
Disable additional caregiver disutility when patient moves to permanent care	[redacted]	[redacted]	£34,056
EAG base case	[redacted]	[redacted]	£82,719

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; NHSE, NHS England; PAS, patient access scheme

Cost-effectiveness results: EAG scenario analyses

EAG scenarios are all substantially higher than £30,000 / QALY

Table: EAG scenario analyses on EAG base case (deterministic ICERs, PAS price)

	Inc. costs	Inc. QALYs	ICER (£/QALY)
EAG base case	[redacted]	[redacted]	£82,719
EAG baseline distribution MCI due to AD and mild AD	[redacted]	[redacted]	£84,707
Infusion costs based on chemotherapy code SB12Z	[redacted]	[redacted]	£57,715
Infusion costs based on company's micro-costing + overhead	[redacted]	[redacted]	£51,215
APOE4 testing costs based on NHS England estimate	[redacted]	[redacted]	£83,151
Include 1 caregiver per patient	[redacted]	[redacted]	£88,622
100% of patients with mild AD in permanent care remain on treatment	[redacted]	[redacted]	£88,289
Use GERAS utility for caregivers + 1.8 caregivers	[redacted]	[redacted]	£86,214

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme

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Equality considerations and aspects not captured in economic modelling

No further issues raised during draft guidance consultation in addition to those that were discussed at ACM2 – see summary of issues discussed at ACM2 in appendix

Abbreviations: ACM, appraisal committee meeting

Managed access (1)

Managed access proposal

DG uncertainties to be addressed:

- Administration costs
- AD progression in long term
- Proportions with MCI and mild AD
- Treatment discontinuation
- Stopping rules

(company deem other uncertainties already addressed or methodological)

Data collection concerns:

- [redacted]
- [redacted]

Company DG2 response:

Company dispute the committee's ACM2 conclusion that the proposed data collection would lead to considerable burden as Clarity AD OLE remains the primary source of potential efficacy data collection

Proposed data sources:

Clarity AD single-arm open-label extension

- Clarity AD patients continue on lecanemab or switch from placebo to lecanemab for up to 4 years
- [redacted]
- [redacted]

Alzheimer's Disease Neuroimaging Initiative (ADNI) database

- Used to construct long-term placebo arm for Clarity AD

Real-world NHS England clinical data

- [redacted]
- [redacted]
- [redacted]
- Expected lecanemab population in NHS England:
  Year 1 ([redacted]) → Year 3 ([redacted]) → Year 5 ([redacted])

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment

Managed access (2)

Managed access team feasibility assessment

Abbreviations: MRI, magnetic resonance imaging; NHSE, National Health Service England

Key issues	Likelihood data could resolve uncertainty	Comments and questions to committee and experts
Significance of treatment effect	MED to HIGH	Proposed to be gathered in ongoing trial, is the trial likely to resolve this uncertainty?
Estimating long term outcomes	MED to HIGH	Proposed to be gathered in ongoing trial, data collection in clinical practice would likely not be longer than the trial
Treatment discontinuation	LOW - MEDIUM	• Company proposes gathering [redacted], as well as the [redacted], both in the trial and in clinical practice. • Is data collection in clinical practice practicable for NHSE and without undue burden?
Model starting distribution	MEDIUM	Company proposes gathering [redacted] Is this practicable for NHSE and without undue burden?
Costs: infusion costs	LOW	The company suggests a [redacted] could be conducted to resolve this. Is this practicable for NHSE and without undue burden?

Managed access (3)

Managed access team consider several uncertainties may be reduced

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for routine use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

Managed access team comments:

- Overall, the company's proposal does provide a route to reducing several of the draft guidance uncertainties
- NHSE considers the following components as uncertain:
  - Estimated population – would require data collection to establish numbers moving through the pathway
  - Stopping rule – proposed stopping rule in residential care is inappropriate, treatment could still be effective

If managed access is considered suitable, committee should establish:

- Which uncertainties should be addressed in managed access – does managed access need the full proposal to be implemented to have value? For which uncertainties would NHSE data collection be essential?
- Which baseline characteristics should be collected (CDR-SB, subgroup status, EQ-5D-5L...)?

Abbreviations: CDR-SB, Clinical Dementia Rating scale Sum of Boxes; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels NHSE, NHS England

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease

- ❑ Background and ACM1 recap
- ❑ Consultation responses (excluding company)
- ❑ Company response and key issues
- ❑ Cost-effectiveness results
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issue to discuss	Key question for committee	Slide
Alignment with ID6222	Are the changes made to align ID4043 and ID6222 appropriate?	11
Transition probabilities	Would lecanemab affect the proportion of people who progress from mild to severe dementia?	12
Stopping rule for residential care	Would people with MCI or mild AD have lecanemab in residential care?	13
Stopping rule for disease progression	Would progression be monitored at routine infusion visits, or additional monitoring needed?	14
Treatment waning	How should treatment waning be included in the model?	15
Infusion costs	How should infusion costs be included in the model?	17
APOE4 testing costs	What unit cost should be used for APOE4 testing costs?	18
Utility values	What approach for carer utility values should be used?	19

Abbreviations: ACM1, appraisal committee meeting 1; EAG, evidence assessment group; MCI, mild cognitive impairment

NICE National Institute for Health and Care Excellence

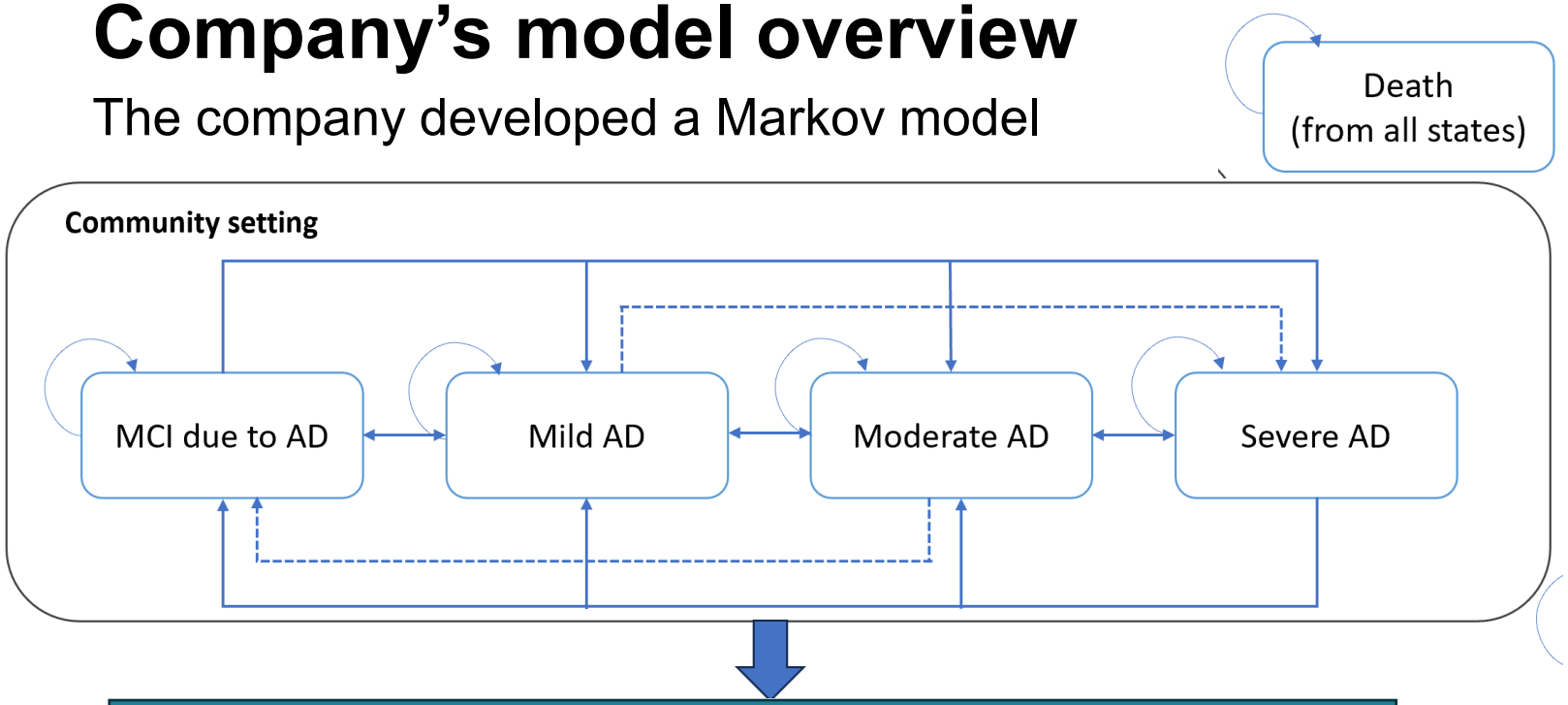
Thank you.

Supplementary appendix

NICE National Institute for Health and Care Excellence

Company's model overview

The company developed a Markov model



Separate but identical model is used for the residential care setting also

- Markov state transition model in which people progress through 4 AD health states based on disease severity, in the community and residential care settings.
- Health state membership derived using cohort simulation in discrete time.

- Technology affects **costs** by:
  - Increased acquisition costs
  - Increased administration costs
  - Increased monitoring costs
- Technology affects **QALYs** by:
  - Increasing time spent in MCI and mild AD community setting
  - Slowing disease progression
- Assumptions with greatest ICER effect:
  - Assuming no treatment effect for people who stop treatment
  - Costs and resource use
  - Stopping rules

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; QALY, quality-adjusted life year

Committee preferred assumptions at ACM2

Committee preferred assumptions

- Model structure acceptable for decision making
- Modelling backward transitions appropriate
- Multistate survival analysis for transitions that change over time for 18 months appropriate
- General population mortality for MCI appropriate
- Residential care stopping rule not appropriate
- Reducing non-medical health-state costs by 47.2% to remove private care costs appropriate
- Appropriate for amyloid beta testing: 90% have lumbar puncture, 10% have a PET CT scan, 28.8% will not have amyloid pathology
- Mixed effects models with repeated measures to estimate utilities acceptable
- Patient-reported EQ 5D for MCI and mild dementia health states acceptable
- Treatment-independent utility values appropriate
- Incremental approach for carer utility acceptable

Consultation responses – patient organisations

Alzheimer's Research UK:

- 3 clinicians estimated lecanemab infusion costs to be £250 to < £500
- NICE, NHS England, and the company should continue exploring the possibility of managed access
- True impact on carers' quality of life is not being incorporated
- Would like to explore a non-reference case to more accurately reflect significant costs to unpaid carers
- Concern that lecanemab not eligible for the severity modifier given significant disease burden

Alzheimer's Society (no new evidence to submit further to consultation on the first draft guidance)

- See previous consultation responses here

Consultation responses – professional organisations

UK Clinical Pharmacy Association:

- Lecanemab has moderate gains vs risk and burden, so investment in improving pathways and care overall may be better than investing in individual medicines
- Clarification on implication of genetic testing needed and pathways that support patients and families
- Lack of diversity in trials is a widespread issue across healthcare research
- Significant burden for infusion units, many infusion units are already at full capacity
- Focus should be on appropriate resource allocation across diagnosis, treatment, and cessation
- Encourages real-world data collection through partnerships to allow pathway modifications if needed

Association of British Neurologists:

- Data does not show a trend for patients to present at an earlier stage over time, but many experts believe there will be a shift to earlier presentation as public awareness of treatments grows
- Blood test for Alzheimer's pathology now available in UK but is not recommended by manufacturer for checking treatment eligibility, but it could maybe be used to rule out some people from further testing
- Concerned about face validity of carer utility values (virtually identical in MCI, mild AD, and moderate AD)
- Lecanemab stopping rule should be easy to implement as treatment follow-up will be carried out anyway
- Support a recommendation in managed access

Abbreviations: AD, Alzheimer's disease

Consultation responses – professional orgs and others

Royal College of Psychiatrists:

- Blood-based biomarkers offer comparable performance to both CSF and amyloid-PET biomarkers
- Suggest 18-month stopping rule – shorter than the MHRA licence but consistent with donanemab's licence and pivotal lecanemab trial
- Cause of AD is uncertain and ultimately to move beyond current symptomatic treatments progress will be stepwise and most likely modest
- Need for more accurate diagnostic and novel treatment pathways

UCL Dementia Research Centre:

- Awareness of disease-modifying treatments will lead to individuals coming forward earlier to seek advice about cognitive complaints, likely to increase the proportion of people seeking advice at an MCI stage
- EQ-5D scores (from GERAS study and used for donanemab) appear very far from clinical expert opinion
- Conducted a survey of attendees at the Alzheimer's Research UK Conference (March 2025)
  - Mean QoL rating having a partner with **mild** dementia **0.58** (n=254), with **severe** dementia **0.27**
  - Mean QoL rating *themselves* having **mild** dementia **0.51** (n=250), having **severe** dementia **0.08**
- Most people starting treatment would very likely have someone living with them, minimum 1 carer per person

Abbreviations: MCI, mild cognitive impairment

NHS England consultation response from ACM2

Previous approach to estimating lecanemab infusion costs

Previous infusion cost: £565

- No NHS price for infusion, so estimated from current coding guidance to reflect most likely cost charged
- Person's diagnosis and day attendance are primary drivers of cost, rather than the procedure itself
- Assumed that appropriate OPCS code is X292: Continuous IV infusion of therapeutic substance NEC

Updated approach to estimating lecanemab infusion costs

Updated infusion cost: £432

- Inappropriate to use chemotherapy infusion cost as a proxy for lecanemab
- Lecanemab requires more complex preparation, carries a higher risk of adverse infusion reaction, will be used in older people who may also have more complex needs
- Not possible to accurately estimate lecanemab infusion cost because it is not used in clinical practice and activity in research settings is not comparable to NHS clinical practice
- Suggest assuming the same infusion cost as with COVID monoclonal antibody infusion pricing:
  - Pricing supported by bottom-up costing work based on actual clinical practice
  - Reflects specific resource implications of a monoclonal antibody (like lecanemab) and not other drugs
  - Possible for this code to be actually used when administering lecanemab in NHS practice

Abbreviations: AD, Alzheimer's disease

Alzheimer's Society consultation response to DG1

Alzheimer's Society new evidence:

- Diagnosis and treatment for dementia makes up 1.4% of dementia healthcare costs, compared to unplanned hospital admissions which make up almost a third - shows lack of preventative care
- 1 million people with dementia in the UK, set to rise to 1.4 million by 2040
- People with dementia: 50% have mild dementia, 37% moderate dementia, 13% severe dementia
- A&E attendances 3x greater for people with undiagnosed dementia versus similar people without dementia
- Average hospital stay: 9.3 days for mild dementia, 27.7 days for severe dementia
- Average cost of dementia per person per year: £29,000 mild, £43,000 moderate, £81,000 severe
- Delaying admission to residential care leads to savings of up to £9,000 to £45,000 per eligible person
- 147,000+ people are working age carers for a person with dementia and 112,540 no longer in employment
- 39% of carers for people with dementia provide 100+ hours of care a week, 60% provide 35 hours+

Abbreviations: A&E, Accident and Emergency

Consultation responses – online web comments

"Recommendation is suitable" – 2 responses

- Marginal benefits demonstrated in clinical trials do not currently outweigh the costs long-term treatment effect that is below the level considered to be evidence of minimal clinical benefit
- Uncertainty in either meaningful or long-term treatment effect because open label extension trial data shows treated and untreated groups have the same rate of decline
- Appropriate to not recommend for managed access as cost of evidence generation would result in funding for established services being diverted to fund an unproven treatment
- If approved in the future, vital that a suitable funding variation is put in place to ensure system readiness

"Recommendation is not suitable" – 1 response

- Not taken into account the effect of Alzheimer's on the patient's family or on society as a whole
- The longer someone stays in the mild phase of dementia, the cheaper the cost of care is to society
- Recommendation stops the NHS from researching the long-term effects of the drug and increases the cost of care which is borne by the social services and the NHS

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment

Background on Alzheimer's disease

Alzheimer's is a progressive brain disease, the most common type of dementia

- Dementia is leading cause of death in UK, Alzheimer's affects 6 in 10 people with dementia
- Age is largest risk factor and risk of mild cognitive impairment (MCI) and mild dementia increases with age

80,000 people in England diagnosed with mild dementia due to Alzheimer's	~5% of people over 65 and ~25% of people over 80 have MCI but exact number unknown	More than a third of people with dementia in England do not have a diagnosis

- Alzheimer's is thought to be caused by abnormal build-up of proteins in the brain (such as beta-amyloid) → amyloid deposits form plaques and disrupt the function of brain cells
- NIA-AA guidelines are used in the pivotal trial to diagnose Alzheimer's disease:

MCI due to Alzheimer's:
mild changes in memory and thinking are noticeable and measurable, but do not disrupt a person's day-to-day life

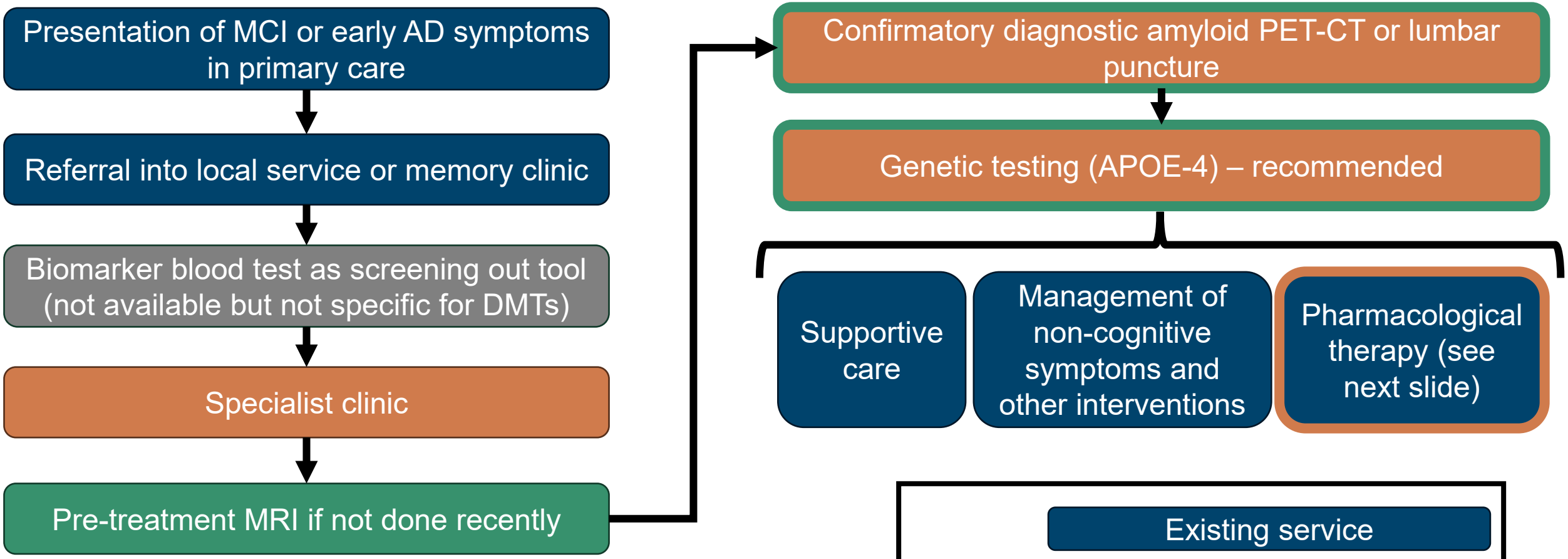
Dementia due to Alzheimer's:
impairments in memory, thinking and behaviour decrease a person's ability to function independently in everyday life

- Apolipoprotein E-4 (APOE-4) gene increases an individual's risk for developing Alzheimer's disease

Abbreviations: APOE, apolipoprotein E; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging and Alzheimer's Association

Diagnostic pathway

NHSE proposed diagnostic pathway - new elements needed for DMTs highlighted



Abbreviations: AD, Alzheimer's disease; APoE4, apolipoprotein E 4; CT, computed tomography; DMT, disease modifying treatment; MCI, mild cognitive impairment; MRI, Magnetic resonance imaging; NHSE, NHS England; PET, positron emission tomography

Treatment pathway

Current treatment pathway with new treatments highlighted

Current treatments for each AD stage plus proposed positioning of lecanemab

Mild cognitive impairment

- Lecanemab

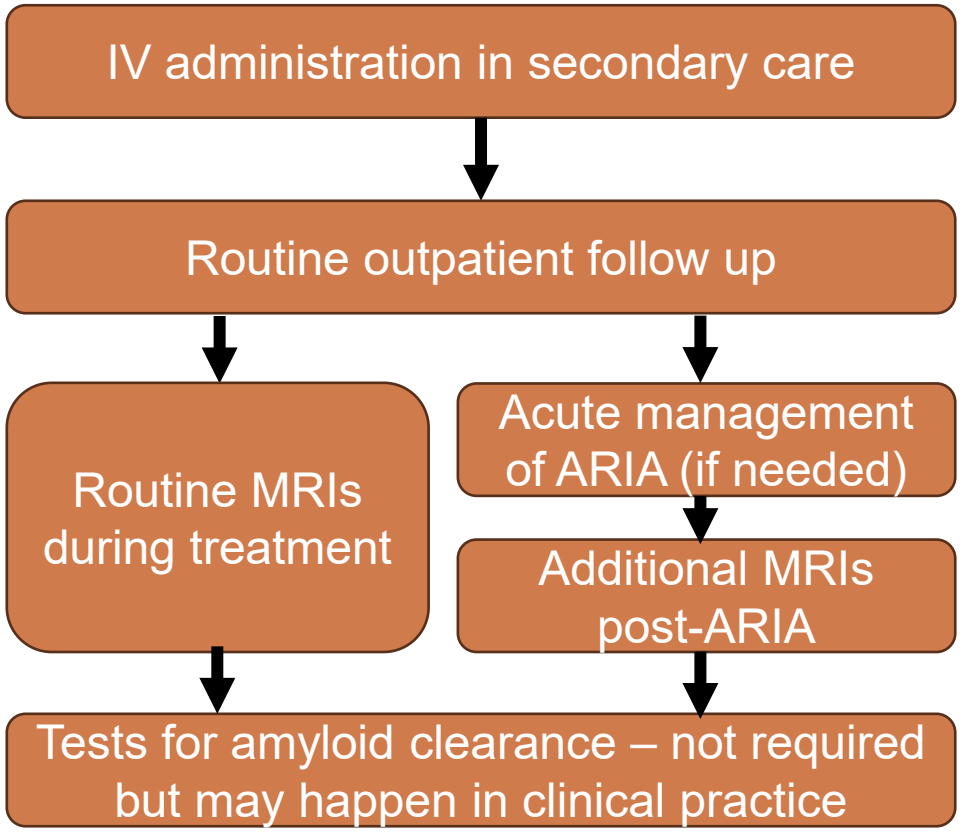
Mild AD

- AChEI monotherapy (donepezil, galantamine or rivastigmine)
- Lecanemab

Moderate to severe AD

- **Moderate or severe AD:** AChEI + memantine
  Moderate AD if AChEI intolerant / contraindicated: memantine monotherapy
  Severe AD: memantine monotherapy

Treatment pathway specific to lecanemab



Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; ARIA, Amyloid-related imaging abnormalities; MRI, Magnetic resonance imaging

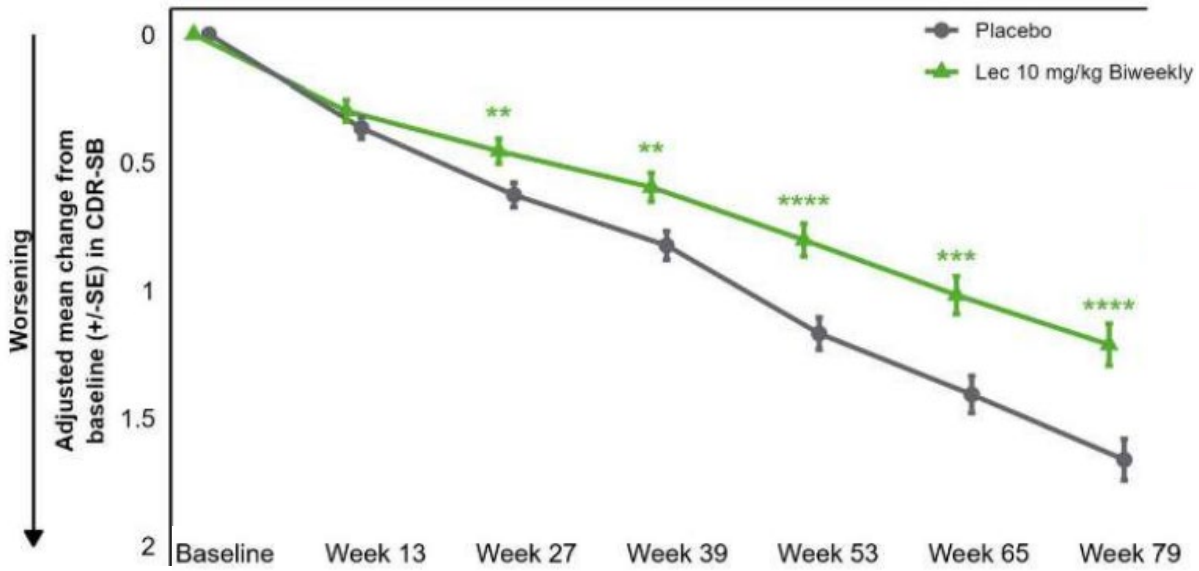
Key clinical trial results

Lecanemab reduces decline in CDR-SB by 27% at 18 months

Clarity AD: mean CDR-SB and difference at 18 months

Clarity AD statistic	Lecanemab	Placebo
N (baseline)	859	875
N (week 79)	714	757
Mean change from baseline	1.213	1.663
Mean difference (between arms)	-0.451	
95% CI for differences	-0.669 to -0.233	
p-value	0.00005	
% Difference vs. placebo	-27.1%	

Adjusted mean change from baseline in CDR-SB – ITT FAS+



** p<0.01, *** p<0.001, **** p<0.0001

Faculty of Public Health comments

- Evidence suggest minimum clinically important CDR-SB difference in MCI of 0.98; 1.63 in mild AD
- Effect is half of what is considered meaningful
- Lecanemab effect at 18 months is about half of the effect of current drugs when used for 6 months

Royal College of Psychiatrists comments

- Trial shows meaningful but modest clinical benefit
- "Time saved" of 4-6 months is clinically meaningful
- Very limited data on long term cumulative benefits

Association of British Neurologists comments

- Consider the benefits clinically meaningful
- If trial evidence is confirmed over longer-term, expect potentially significant meaningful benefits

- ➢ All key secondary endpoints (change at 18 months in amyloid PET Centiloids, ADAS-Cog14, ADCOMS, ADCS MCI-ADL) showed statistically significant results favouring lecanemab
- ➢ ($p<0.001$) beyond 6 months for all endpoints

Infusion costs: NHSE process for estimating costs

1. Define activity as continuous IV infusion of therapeutic substance in combination with monoclonal antibodies bands 1 and 2
2. Extract data from secondary user services dataset for elective and day case and outpatient attendance
3. Remove non-elective zero price HRG activity (no price recorded)
4. Limit Admitted Patient Care (APC) elective spells length of stay to zero or 1
5. Calculate average price and uplift in line with NHS tariff inflation
6. Apply average market forces factor (MFF)

Utility values from ACM2

Table: Source for health state utility values used in the economic analysis

			MCI	Mild AD	Moderate AD	Severe AD
Community setting	**Patient**	Lecanemab	[redacted] (P)	[redacted] (P)	[redacted] (P)	[redacted] (P)
		Placebo	[redacted] (P)	[redacted] (P)	[redacted] (P)	[redacted] (P)
	Carer	Lecanemab	[redacted] (S)	[redacted] (S)	[redacted] (S)	[redacted] (S)
		Placebo	[redacted] (S)	[redacted] (S)	[redacted] (S)	[redacted] (S)
Residential setting	**Patient**	Lecanemab	[redacted] (S)	[redacted] (S)	[redacted] (P)	[redacted] (P)
		Placebo	[redacted] (S)	[redacted] (S)	[redacted] (P)	[redacted] (P)
	Carer	Lecanemab	[redacted] (S)	[redacted] (S)	[redacted] (S)	[redacted] (S)
		Placebo	[redacted] (S)	[redacted] (S)	[redacted] (S)	[redacted] (S)

Clarity AD / MMRM

Farina et al. 2020

Black et al. 2018

P = patient-by-proxy

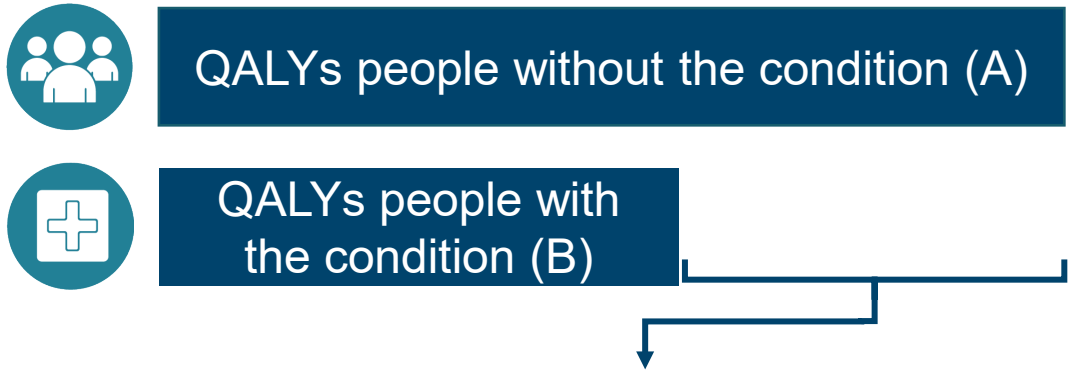
S = self-reported

Company summary of literature on adaptation effect:

- Conde-Sala et al. found that adaptation may contribute to QoL differences in early AD as positive patient ratings might be psychological mechanisms, the disability paradox, or “self-maintaining” and “self-adjusting”
- Negative carer ratings explained by diagnosis impact and changes in the patient leading to greater burden
- Adaptation does not explain differences in later stages, patients ‘overly positive’ due to neurological deterioration
- Aligns with Landeiro et al.: patients with severe AD self-reported high utilities, but patient-by-proxy utilities lower
- Adaptation in this context not mentioned in NICE guidance before, but proxy utility values accepted in TA217

QALY weightings for severity at ACM1

Severity modifier calculations and components:



QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

	QALYs without condition	QALYs with condition	**Absolute QALY shortfall**	**Proportional QALY shortfall**
Company base case	8.78	4.58	**4.20**	**0.48**

Company does not make the case for a severity modifier to be applied due to its base case not meeting the thresholds

Abbreviations: QALY, quality-adjusted life year

Equality considerations

No further issues raised during draft guidance consultation

Key themes are prevalence, diagnosis and treatment of AD and NHS capacity

Inequality in diagnosis and accessing care

- Biomarker diagnosis for lecanemab will act as a barrier to treatment thus increasing health inequalities
- The following groups are already underdiagnosed:
  - People from deprived areas, rural areas, ethnic minority backgrounds, prisoner populations
- Regional variation in diagnosis rates from 50% to 90%
- People with more agency and resources will find it easier to 'adhere' to the complex diagnosis pathway

NHS capacity and service delivery considerations

- NHS capacity likely to impact access to lecanemab
- Opportunity cost would increase health inequalities as services under existing strain would be required to deliver this treatment

Treatment effectiveness and benefits may be different for some subgroups

- Lecanemab clinical trial showed benefits may vary by age, sex and family background

Groups that have not been fully represented in the trial, risking access to care

- People with Down's syndrome have a 90% lifetime risk of Alzheimer's but were excluded from the trial
- Some people with young-onset dementia due to trial lower age-limit of 50 years excluding them
- Some ethnic groups were under-represented in trial

Abbreviations: AD, Alzheimer's disease

Aspects not captured in modelling

No further aspects raised during draft guidance consultation

Uncaptured impact on patients, carers, and NHS services

Company: measuring quality of life

- Difficulty assessing QoL – literature shows patient-by-proxy utilities in AD tend to be lower than self-reported

Faculty of Public Health: potential false hope

- False hope for people tested but not suitable for treatment
- Emotional burden for people who are APOE-4 carriers
- Lecanemab not a cure and may give some people false hope

Company: impact on carers

- Impact on carers health, finances, and productivity
- Carers grief in 'losing their loved one twice' - loss for the person they knew and physical loss of loved one

Company: lecanemab is innovative

- Lecanemab has been designated by the MHRA for the Innovative Licensing and Access Pathway (ILAP)

EAG: effects of testing

- Potential harmful effects of repeated invasive testing (lumbar)

Company: impact of living longer

- Carer QALY trap - lecanemab penalised for keeping people alive as carer disutility applied for longer
- Lecanemab penalised with increased caregiving costs for keeping people alive and in better health

NHSE: impact on NHS services

- Huge increase in primary/secondary care demand which may impact the provision of other services
- Redesign of AD diagnosis and treatment pathway as required components are not used currently
- New infrastructure and training needed: neurology, psychiatry and geriatric medicine clinics

Company: severity modifier

- Early AD treatments not eligible for severity modifier due to age of population and chronic nature of AD, despite being leading cause of death in UK, significant disease burden, and consensus that treatment should aim to extend time in milder disease states

Abbreviations: AD, Alzheimer's disease; APOE-4, apolipoprotein E 4