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

For public – confidential information redacted ([redacted])

Second appraisal committee meeting

Technology appraisal committee D [6 November 2024]

Chair: Dr Raju Reddy

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

NICE National Institute for Health and Care Excellence

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

Lecanemab (Leqembi, Eisai)

First committee meeting held before final marketing authorisation available, committee considered full Clarity AD trial population, including APOE-4 subgroups

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 slow spread of tau in 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 available since first committee meeting

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

Clarity AD was a Phase 3, randomised, placebo-controlled trial of lecanemab

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
Key secondary outcomes	Change in amyloid PET, ADAS-Cog, ADCOMS, ADCS MCI-ADL at 18 months
Locations	North America, Europe, Asia-Pacific, China and UK (8 sites)
Used in model?	Yes

CDR-SB is a 5-point scale used to characterise 6 domains of cognitive and functional performance:

- Memory
- Orientation
- Judgment and problem solving
- Community affairs
- Home & hobbies
- Personal care

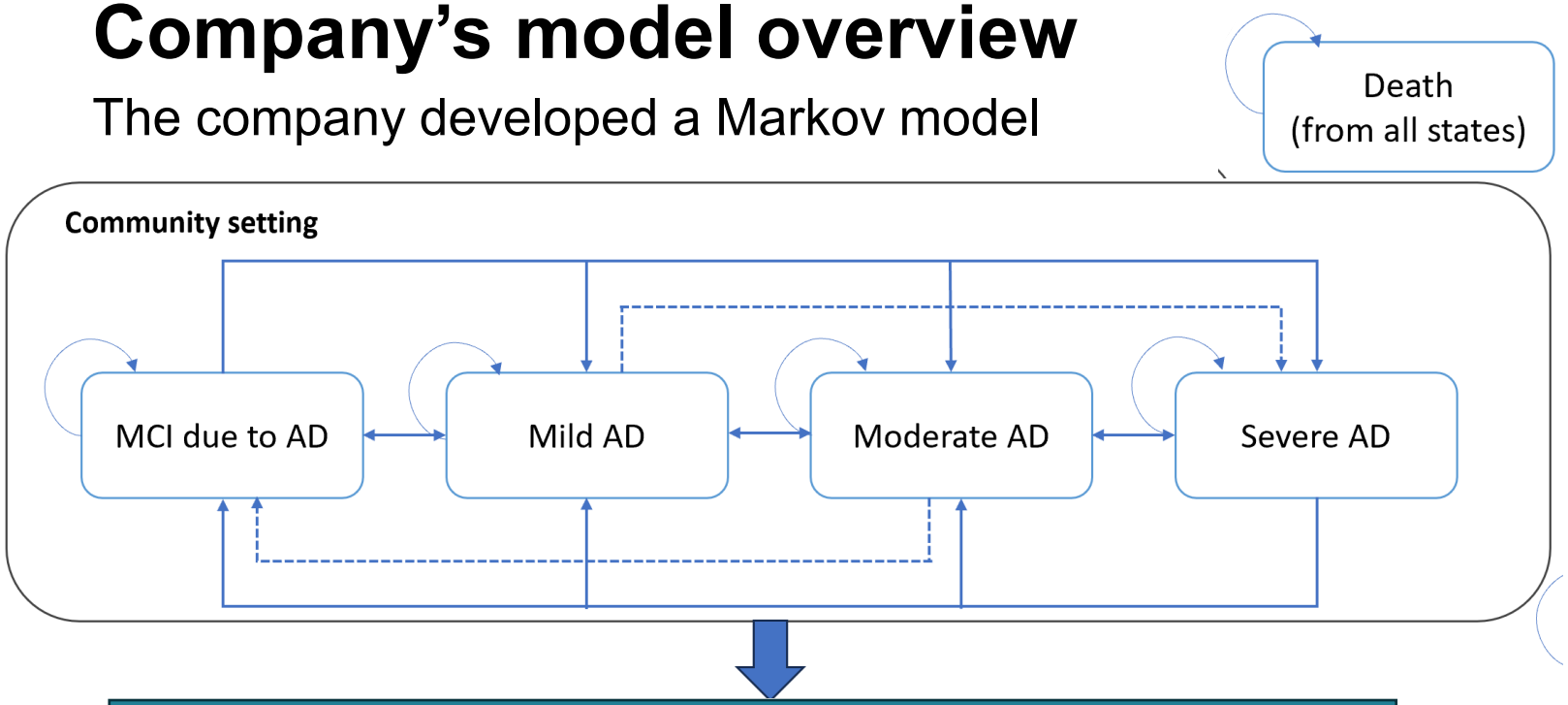
Each domain scored 0 (no impairment) to 3 (severe dementia) and added up.

- Open-label extension (OLE) of Clarity AD underway with up to 4 years of additional data to be collected
- 1st year of additional data already published

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

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 conclusions at 1st committee meeting (ACM1)

Committee recommendation

"The committee recalled the **high uncertainty** associated with the company's model and long-term evidence for lecanemab. It thought that **more evidence was needed** to generate robust cost-effectiveness estimates. It recalled that the EAG's and company's base cases were associated with uncertainty, and that the cost-effectiveness estimates were **above the range** normally considered a cost-effective use of NHS resources. So, it **did not recommend lecanemab** for treating MCI and mild dementia due to Alzheimer's disease in adults who are APOE4 heterozygotes or non-carriers, either for routine NHS use or with managed access."

Committee preferred assumptions

- Model structure acceptable for decision making
- Modelling backward transitions appropriate
- Appropriate to assume that:
  - Amyloid beta testing: 90% lumbar puncture, 10% PET
  - 29% of people tested will not have amyloid pathology

Committee identified uncertainties

- Face validity of transition probabilities
- Impact of treatment discontinuation on outcomes
- How stopping rule for lecanemab would be applied in practice, and impact on costs and outcomes
- Utility values used in the model
- Costs of infusion, testing, and private care

Abbreviations: APOE-4, apolipoprotein E 4; EAG, evidence assessment group; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography

Key issues from 1st committee meeting – to discuss

Key issue at ACM1 (EAG report issue number/s)	Company approach for discussion	ICER impact
Transition probabilities and validity of model outcomes (12, 21)	• Uses evidence assessment group (EAG) preferred multistate model, no constant transition probabilities	Moderate
Treatment discontinuation, potential stopping rules and estimating long term outcomes (5, 13, 15)	• No treatment waning following all-cause discontinuation • Provides requested evidence on progression stopping rule implementation • Still includes a residential care stopping rule	Large
Infusion costs (19)	• Uses updated infusion cost based on company micro-costing study	Large
Utility values (16, 17, 18)	• Uses mixed effects model with repeated measures (MMRM) approach and proxy utility values • Uses new incremental approach to including carer utilities	Large
Mortality for MCI subgroup (14)	• Uses mortality hazard ratio for MCI reported by Crowell et al. to produce mortality outcomes closer to the trial	Moderate

Abbreviations: ACM1, appraisal committee meeting 1; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment

Key issues from 1st committee meeting – resolved or in appendix

Key issue at ACM1 (EAG report issue number/s)	Status
Clinical significance of treatment effect (6)	**Appendix:** company provided requested results and analyses
Comparators (2, 3)	**Resolved:** committee concluded at ACM1 it is acceptable to use SoC from Clarity AD
Trial generalisability (7)	**Appendix:** updated patient numbers to align with EAG base case
Starting distribution in model (11)	(See trial generalisability issue)
Clinical effects by subgroup: age and APOE-4 carrier status (4, 8, 10)	**Appendix:** company provided requested results and analyses
Costs: amyloid beta testing (1)	**Resolved:** committee concluded at ACM1 that company testing approach is appropriate
Costs: tests, MRIs and appointments (9, 19)	**Resolved:** not discussed at ACM1 due to small ICER impact
Costs: removing costs outside of reference case perspective (20)	**Appendix:** company updated figures to remove private care costs in a scenario, EAG accepted

Abbreviations: ACM1, appraisal committee meeting 1; APOE-4, apolipoprotein E 4; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; SoC, standard of care

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

Consultation responses – patient and professional orgs (1)

Association of British Neurologists:

- Unclear what drives cost-effectiveness because draft guidance heavily redacted
- Should exclude costs of diagnostic tests which should already be done for patients per NICE guidelines
- Unclear why severity modifier was not applicable
- Unclear to what extent model includes informal care costs and impacts on quality of life for carers, encourage a non-reference case approach to reflect these significant costs accurately
- Encourage further discussions on managed access and ongoing reviews of long-term data

Alzheimer's Research UK:

- Encourage further discussions on managed access and ongoing reviews of long-term data
- Shared infusion costs (discussed in later slides)
- Uncertain how model incorporated and considered quality of life of carers
- Uncertainty over how stopping rule would work in practice
- Concern that lecanemab not eligible for the severity modifier

Consultation responses – patient and professional orgs (2)

College of Mental Health Pharmacy:

- Recommendation is suitable and considers all relevant evidence
- Need to consider huge burden of Alzheimer's disease as UK “biggest killer” and needs of society, and huge potential costs and impact on system
- Any recommendation should consider barriers to accessing treatment
- Need longer term data which will be gathered only via managed access

Alzheimer’s Society:

- Encourage monitoring of longer-term data and real-world evidence
- Preventative care for Alzheimer's disease is not prioritised
- Consider inequalities due to significant service impacts and people excluded from Clarity AD trial
- Summarised new evidence gathered since previous submission, which covers:
    - Forecast for Alzheimer’s disease population, including for mild, moderate and severe dementia
    - Healthcare resource utilisation and care costs by dementia severity
    - Carer population size and scale of economic impact on carers

Abbreviations: AD, Alzheimer's disease

Consultation responses – patient and professional orgs (3)

Royal College of Psychiatrists:

- Propose assessing cost-effectiveness of:
  - 18-month stopping rule
  - limiting recommendation to APOE-4 non-carriers
- Lecanemab may be cost-effective with subcutaneous formulation and blood biomarkers for amyloid

Faculty of Public Health:

- Only 20% of dementia attributable to Alzheimer's disease (not 60% as reported in draft guidance)
- Guidance bases following points on clinical expert opinion and not empirical evidence:
  - All people with amyloid positivity have or will develop Alzheimer's disease
  - All people with MCI will progress to dementia
  - Lecanemab is disease-modifying and slows disease progression by 4 to 6 months
  - 0.451 difference in Clinical Dementia Rating scale Sum of Boxes is clinically meaningful
- People in trial likely experience functional unblinding and so identify their treatment, biasing results
- Disagree that Clarity AD trial cohorts are generalisable to the UK

Abbreviations: MCI, mild cognitive impairment

Consultation responses – online web comments

"Recommendation is suitable" – 10 responses

- Lecanemab benefits are small, uncertain and inconsistent, might be entirely due to a placebo effect
- Benefits too small to justify high costs which would divert resources from other treatments
- Considerable concerns with safety and efficacy
- Recognise huge system impact on NHS if recommended, would need sustainable funding
- Large proportion of people tested and not eligible would seek out further health care resources due to testing
- Want to see whether access can be given for a subset of people who would see benefit
- Any positive guidance would need clear stopping rules
- Guidance incorrectly states that MCI always leads to AD

"Recommendation is not suitable" – 4 responses

- Cost savings have not been considered, delaying residential care for 1 year saves £60-80,000 per person
- Lecanemab should not be penalised because the NHS is not ready for the service impact
  - Diagnostic costs should be excluded as they should be done for all patients as per NICE guidelines
- Lecanemab would slow disease progression by more than 4 to 6 months when given with other treatments
- Inappropriate to exclude informal care
- Inequality concerns as people can currently access lecanemab only through private health care
- Infusion cost estimates too high, unit costs would reduce when services used more often
- Lecanemab is the first disease modifying drug for AD, must be flexible

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

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

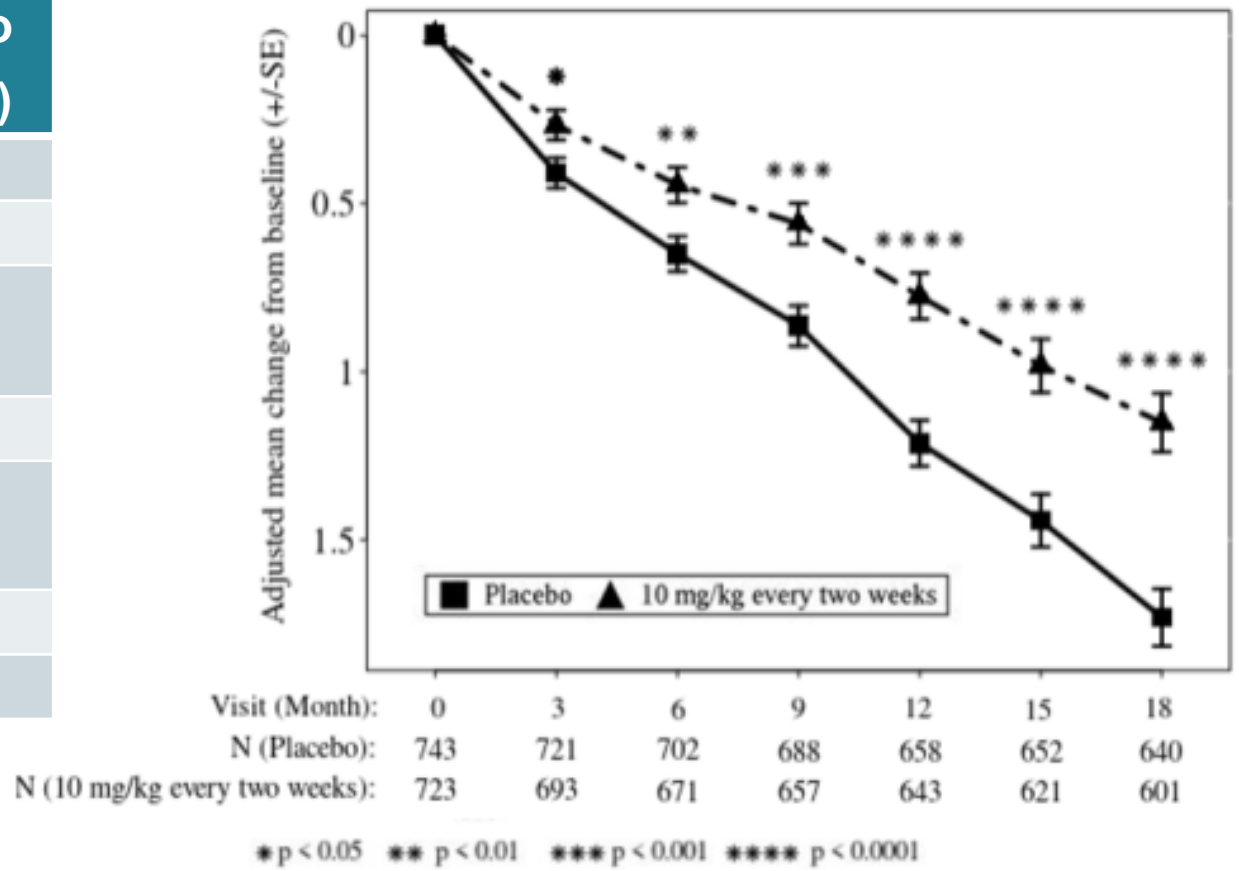
Clinical effectiveness results (indicated population)

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

Clarity AD: Change from baseline in CDR-SB score at 18 months – MMRM

Clarity AD Statistic	Lecanemab (n= 723)	Placebo (n= 743)
N (baseline)	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]
Adjusted mean (SE)	1.151 [redacted]	1.730 [redacted]
Adjusted mean difference	-0.579	
95% confidence interval	-0.811 to -0.347	
p-value	<0.00001	
% Difference vs. placebo	-33%	

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



Abbreviations: CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MMRM, mixed effects model with repeated measures; SE, standard error

Changes to the company base case for ACM2

Assumption	Company base case
Population	• Aligns with marketing authorisation population (exclude APOE-4 homozygotes) • Accepts EAG preference of distribution of people with MCI or mild AD
Adverse events	• Removes serious AEs, due to double counting because of overlap in the classification of severity and seriousness in Clarity AD • Serious AEs already captured in model through AE data included by severity grades
Transition probabilities	• Uses multistate survival model to estimate transition probabilities and incorporate time-dependent transitions (suggested by EAG and committee)
Mortality	• Uses mortality hazard ratio for MCI reported by Crowell et al. to produce mortality outcomes closer to the trial
Treatment discontinuation	• Weights discontinuation rate to MCI and mild AD patients (not requested by EAG or committee) based on number of people in each group
Caregiver utility	• Models caregiver utilities as increments (rather than decrements) to avoid the 'carer QALY trap' which penalises extended survival time
APOE-4 testing costs	• Includes APOE4 testing costs for those who do not go on to lecanemab
Lecanemab infusion costs	• Uses updated infusion cost based on company micro-costing study with 3 experts with lecanemab experience (£139.12)

NICE

Abbreviations: AD, Alzheimer's disease; AE, adverse event; APOE-4, apolipoprotein E 4; EAG, evidence assessment group; MCI, mild cognitive impairment; QALY, quality-adjusted life year

Key Issue: Transition probabilities and model validity

Committee wanted to see transitions that had better external validity

Committee at ACM1

- Unsure about assumption of constant transition probabilities, want to see model produce results in line with trial

Company

- Evidence of time-dependency in hazard plots; so, company adopts multistate survival model in updated base case to estimate time varying transition probabilities (aligns with EAG preferences)
- Based on fit to Clarity AD trial data, uses Weibull distribution for transitions 1-3, exponential for transition 4*
- Base case mortality HR for MCI from Crowell et al. (0.63), not general mortality, as results closer to Clarity AD
- Modelled health state occupancy aligns with Clarity AD at 18 months within [redacted] for both arms
- Scenario: Clarity AD open label extension transitions for months 18 to 36, natural history data for 36 months+

EAG comments

- Company's approach appropriate, but model does not accurately predict state occupancy seen in Clarity AD
- Model underestimates MCI/mild AD, overestimates moderate/severe AD/death, so possible lecanemab bias
- EAG base case assumes no treatment difference for transitions from mild to severe AD as no justification given
- EAG base case uses general population mortality for MCI as Crowell et al. may underestimate mortality
- Scenario with lognormal for transitions 1 and 3 reflects best fit, but not in base case due to decreasing hazards

*Transitions: 1 (MCI to mild AD), 2 (mild to moderate AD), 3 (mild AD to MCI), 4 (moderate to mild AD)

Abbreviations: ACM1, appraisal committee meeting 1; AD, Alzheimer's disease; EAG, evidence assessment group; HR, hazard ratio; MCI, mild cognitive impairment

Is the company's updated model appropriate for decision-making?

Key Issue: Stopping rules

Committee was uncertain how a stopping rule would work in practice

Committee at ACM1

- Not appropriate to apply a lecanemab stopping rule based on entry to residential care due to health inequalities
- Want more information on how stopping rule based on progression to moderate disease would be applied in practice (stopping rule is in the marketing authorisation)

Company

- 3 clinical experts think monitoring would not be resource intensive (tests done alongside infusion visits)
- [redacted]
- Stopping at moderate AD is feasible and practical, provided scenario analysis with quarterly monitoring (not adopted in main base case as costs might be overestimated if tests are carried out alongside infusions)
- Experts say treatment would stop if entering residential care due to disease, not for other reasons
- Provide scenario where 10% of people in residential care continue lecanemab

EAG comments

- Implementing a stopping rule around disease progression uncertain; must include any monitoring costs
- EAG base case uses progression stopping rule and includes quarterly monitoring costs from company scenario
- People with mild AD in model can enter residential care, but company did not include reasons for why people move to residential care (due to disease changes or otherwise), so EAG exclude this stopping rule in base case

Abbreviations: ACM1, appraisal committee meeting 1; AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; EAG, evidence assessment group; HR, hazard ratio

How should stopping rules be modelled?

Key Issue: Treatment effect after discontinuation

Committee considered treatment waning was uncertain, but asked for more info

Committee at ACM1

- Inappropriate to assume that people with MCI or mild AD who stop treatment have the same treatment benefits as people who continue treatment; want scenarios that explore waning of treatment-effect

Company

- No waning applied; no-one in Clarity AD stopped due to low treatment effect, no one lost treatment response
- EAG in TA217 did not apply waning; literature says to exclude waning when "lasting benefit" plausible
- Experts at ACM1: "highly implausible that a person's condition will immediately worsen after stopping treatment"
- Experts post ACM1: continued effect while plaque levels are low, re-accumulation rate of amyloid is slow
- Most common waning start point in NICE appraisals is 5 years, so scenario where [redacted]
- Provide scenario with [redacted]

EAG comments

- People who discontinue study drug may have lost treatment response (even if not the reason for discontinuing)
- Company scenario uses arbitrary values and should be applied to residential care states too; unsure if correctly implemented; EAG assumes 75% treatment effect for off-treatment MCI and mild AD states
- EAG base case uses discontinuation rate from 36-month OLE data after 18-months

Abbreviations: ACM1, appraisal committee meeting 1; AD, Alzheimer's disease; EAG, evidence assessment group; MCI, mild cognitive impairment; OLE, open label extension

How should treatment discontinuation and treatment waning be included in the model?

Key Issue: Infusion costs

Difference in costs estimated by the company and NHS England

Committee at ACM1: Company estimate (£207.59) different to NHSE (£565), so requested further information

Company

- Prefers chemotherapy infusion cost (SB12Z code) used NICE TAs for IV monoclonal antibodies
- 2 of 3 clinicians consulted agreed chemo costs appropriate, none believed NSHE's WD02Z code appropriate
- Used a clinician, nurse, + pharmacist with lecanemab experience to estimate resources for IV infusion with lecanemab, using framework in Burcombe et al. that estimated other IV infusion costs, result: £139.12/infusion

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

NHSE: Focus on singular cost might be inappropriate as average pricing is used, costs for this group might be higher that standard tariff; wrong to use chemotherapy infusion cost as proxy because lecanemab more complex to prepare, more adverse reactions, people have complex needs; cannot use trial infusion cost which is different to NHS clinical practice; suggest using £432 from real world pricing from COVID monoclonal antibody infusion

EAG comments

- Company's quoted infusion costs are lower than costs used in TAs it identified as supporting its approach
- Unsure if using Burcombe et al. is suitable; expert inputs vary substantially in company's micro-costing exercise
- EAG base case uses updated NHSE infusion cost estimates; agrees with NHSE reasoning

Abbreviations: ACM1, appraisal committee meeting 1; EAG, evidence assessment group; IV, intravenous; NHSE, NHS England; TA, technology appraisal

How should infusion costs be included in the model?

Key Issue: Patient and carer utility values

Committee concerned with impact of adaptation effect and proxy utility values

Committee at ACM1

- Requested summary of utility values with justifications, and consideration of adaptation effect and proxy values

Company (provided summary of utility values)

Adaptation effect (people with a chronic condition often self-report QoL as higher than public or carer estimates):

- Provided a summary of adaptation effect in AD in literature
- Scenarios show ICER is not sensitive to using proxy values, so adaptation does not mean decision uncertainty

Carer QoL:

- Use incremental approach for carer utilities, where the 'worst' health state (severe AD, institutional setting) is a reference, and increments are calculated relative to this health state for all other health states
- Means that extended survival time is not penalised and circumvents the carer QALY trap
- QoL underestimated as EQ-5D does not accurately capture carer QoL, model assumes only 1 carer per person

EAG comments

- Company not provided detail to assess implementation of the updated MMRM approach, requests evidence
- EAG base case uses patient reported EQ-5D for MCI and mild AD, removes fixed effects treatment covariate
- Company approach has different carer utility for same health states but different care setting, little evidence to support this so EAG base case removes this difference but uses company's new incremental approach

Abbreviations: ACM1, appraisal committee 1; AD, Alzheimer's Disease; EAG, evidence assessment group; MCI, mild cognitive impairment; MMRM, mixed effects model with repeated measures; QoL, quality of life

What approach for utility and disutility values should be used in the model?

Summary of company and EAG base case assumptions

Differences between company and EAG base cases

Assumption	Company base case	EAG base case
Transition probabilities	• Treatment difference in transitions from mild to severe AD • Mortality HR for MCI from Crowell et al. (0.63)	• No treatment difference in transitions from mild to severe AD • General population mortality HR for MCI
Stopping rules	• Stopping rules for disease progression and entering residential care	• Adds quarterly monitoring costs • Removes residential stopping rule
Treatment discontinuation	• No treatment waning for people who stop treatment in MCI and mild AD states	• Assume 75% treatment effect for off-treatment MCI and mild AD states • Discontinuation rate after 18 months from OLE
Infusion costs	• £139.12 cost from micro-costing	• £432 based on NHSE
Private care costs	• No adjustment for private care costs	• Reduce non-medical costs by 47.2%
Carer utility values	• Use incremental approach and decrement for residential care setting	• Use incremental approach, removes decrement for residential care setting

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; HR, hazard ratio; MCI, mild cognitive impairment; NHSE, NHS England; OLE, open label extension

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

Cost-effectiveness results: revised company base case

Company considers all information confidential, but base case is >£30,000/ 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]	£105,066

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]	£39,525

Changes to company base case:

- Population
- Adverse events
- Transition probabilities
- Mortality
- Caregiver utility
- APOE-4 testing costs
- Lecanemab infusion costs
- Updated PAS price

Abbreviations: APOE-4, apolipoprotein E 4; 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

All company scenarios are higher than £20,000 / QALY

Table: Company scenario analyses (PAS price)

Scenario	Deterministic PAS ICER
Company base case	**£39,525**
Diagnostic testing costs excluded	£38,507
Caregiver utility method: patient and care additive	£25,184
MCI due to AD only	£46,599
Mild AD only	£36,122
Trial based treatment duration scenario	£23,987
Administration cost: SB12Z	£44,139
MMRM-derived utilities (self-reported for patients)	£39,603
Reduce non-medical health state costs by 47.2%	£41,289
Assume 10% patients remain on treatment in institution	£40,178
OLE discontinuation rate after 18 months	£42,016
Include quarterly outpatient appointments	£41,828
Apply treatment effect waning after all-cause discontinuation	£41,325
Clarity AD mortality for 0-18 months	£39,188
Mortality in MCI health state equal to general population	£41,684

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; MMRM, mixed effects model with repeated measures; OLE, open label extension; PAS, patient access scheme

Cost-effectiveness results: EAG base case

EAG base case is substantially higher than £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]	**£39,525**
Treatment effect waning: 75% in MCI and mild AD	[redacted]	[redacted]	£46,273
All cause discontinuation rates from OLE study	[redacted]	[redacted]	£42,016
Disable residential care stopping rule	[redacted]	[redacted]	£41,880
Mortality in MCI = general population	[redacted]	[redacted]	£41,684
Disable carer residential disutility	[redacted]	[redacted]	£42,936
Include quarterly outpatient costs	[redacted]	[redacted]	£41,828
NHSE infusion costs	[redacted]	[redacted]	£59,260
Exclude private care costs (47.2% reduction)	[redacted]	[redacted]	£41,289
Patient reported utility and removed covariate	[redacted]	[redacted]	£39,603
Disable treatment effect in mild to severe AD	[redacted]	[redacted]	£43,377
EAG base case	[redacted]	[redacted]	**£105,559**

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; NHSE, NHS England; OLE, open label extension; PAS, patient access scheme

Cost-effectiveness results: EAG scenario analyses

All EAG scenarios are 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]	**£105,559**
Treatment effect waning: 0% treatment effect immediately upon discontinuation for MCI and mild AD states	[redacted]	[redacted]	£160,225
Treatment effect waning: 100% treatment effect upon discontinuation for MCI and mild AD states	[redacted]	[redacted]	£92,106
HRG code SB12Z for infusion costs (company's chemo code)	[redacted]	[redacted]	£80,430
Lognormal distribution for transitions 1-3	[redacted]	[redacted]	£108,257

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

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

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

Managed access (1)

Company's 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]

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]
- [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 at ACM1 (EAG report key issue number/s)	Key question for committee	Slide
Transition probabilities and validity of model outcomes (12, 21)	Is the company's updated model appropriate for decision-making?	18
Treatment discontinuation and potential stopping rules (15)	How should treatment discontinuation and treatment waning be included in the model? How should stopping rules be modelled?	19 and 20
Infusion costs (19)	How should infusion and private care costs be included in the model?	21
Utility values (16, 17, 18)	What approach for utility and disutility values should be used in the model?	22
Mortality for MCI subgroup (14)	How should mortality for MCI be modelled?	18

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

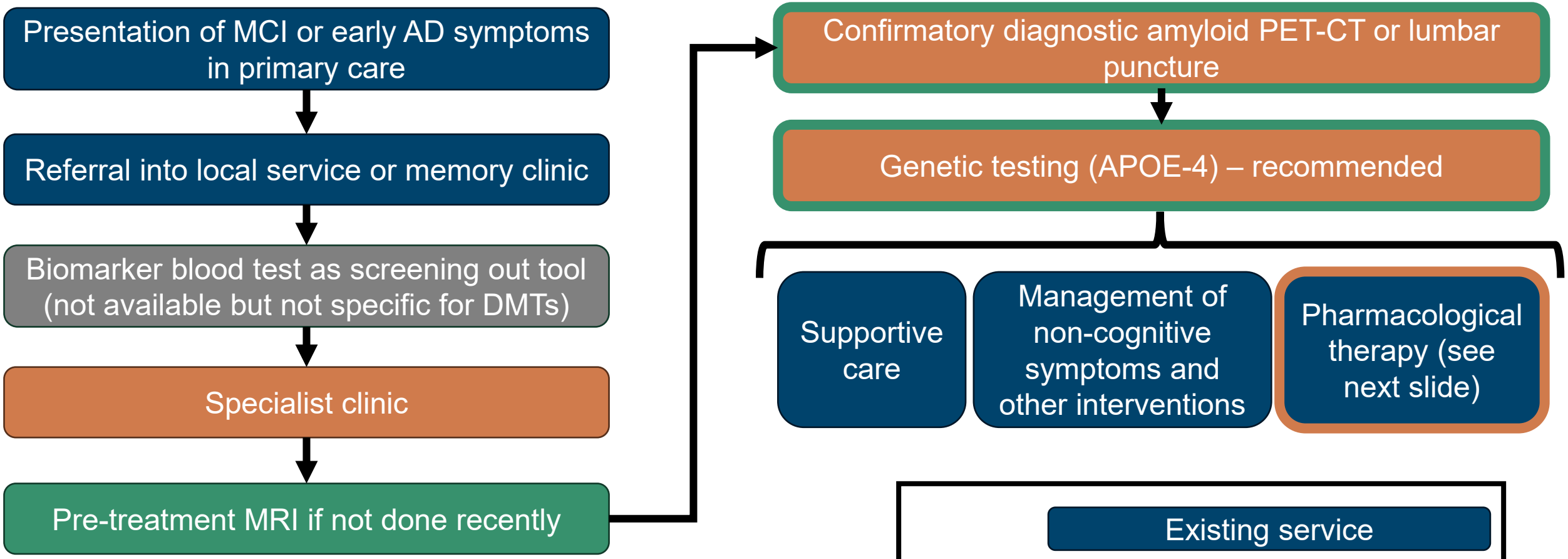
Key issues at ACM1

	Issue (EAG report key issue number/s)	ICER impact
Clinical-effectiveness	Clinical significance of treatment effect (6)	Unknown
	Comparators (2, 3)	Unknown
	Trial generalisability (7)	Unknown
	Clinical effects by subgroup: age and APOE-4 carrier status (4, 8, 10)	Large
Cost-effectiveness	Transition probabilities and validity of model outcomes (12, 21)	Large
	Estimating long term outcomes (5, 13)	Large
	Treatment discontinuation and potential stopping rules (15)	Large
	Costs: infusion and private care costs (19, 20)	Large
	Costs: amyloid beta testing (1)	Small
	Utility values (16, 17, 18)	Large
	Mortality for MCI subgroup (14)	Resolved
Appendix	Starting distribution in model (11)	Moderate
	Costs: tests, MRIs and appointments (9, 19)	Small

Abbreviations: APOE-4, apolipoprotein E 4; MCI, mild cognitive impairment; MRI, magnetic resonance imaging

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

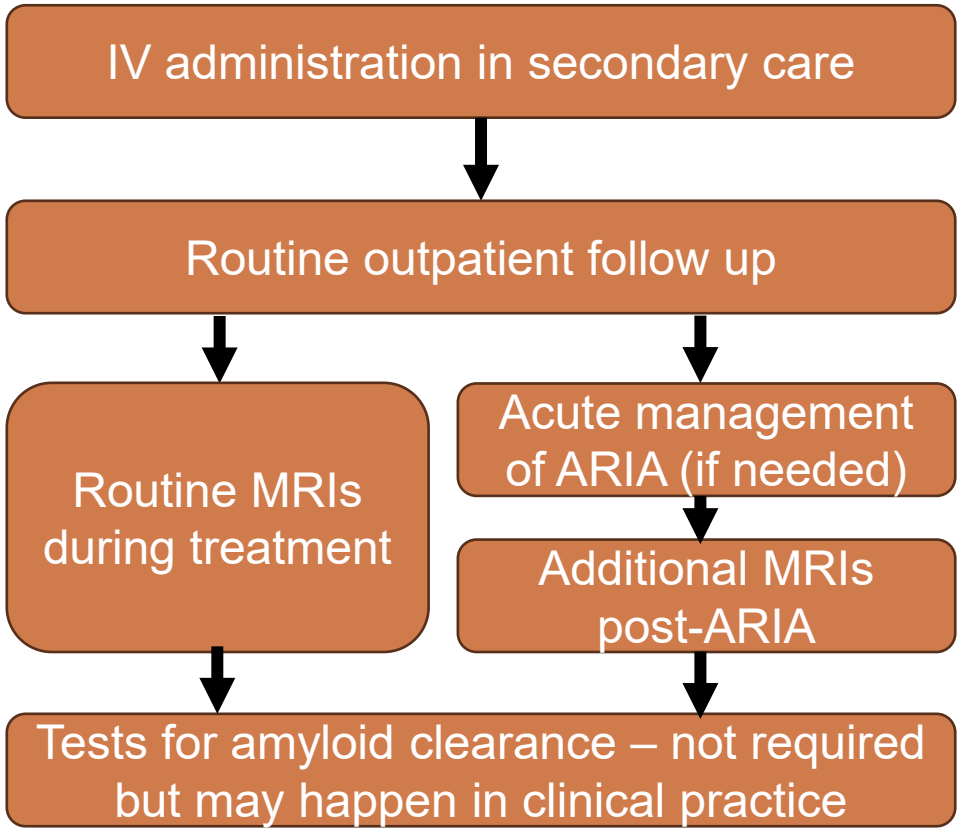
Mild AD

- 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

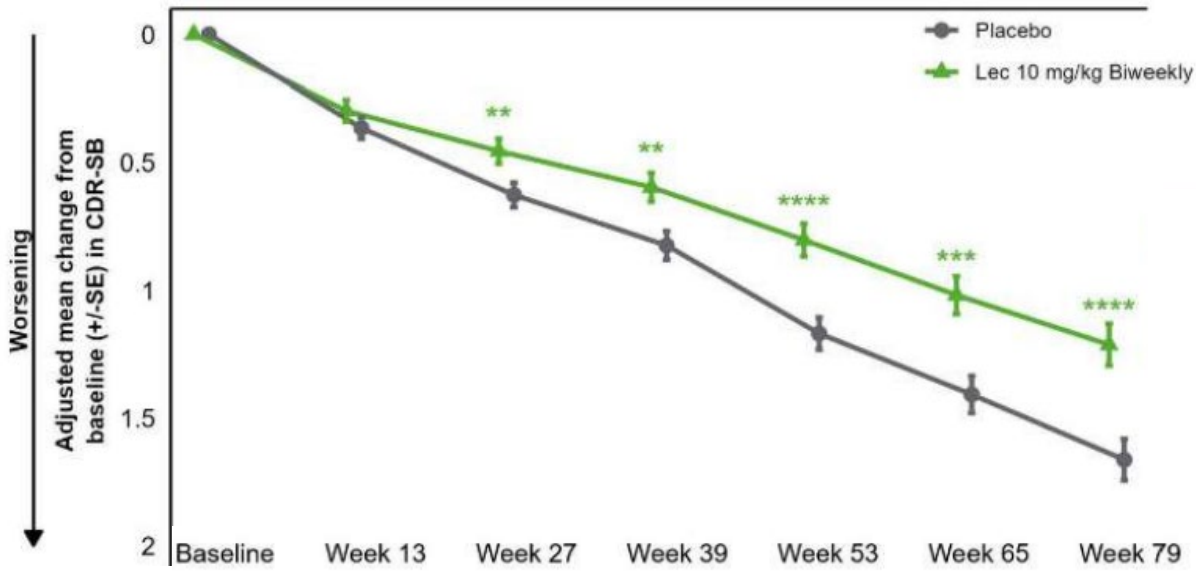
Key clinical trial results

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

How company incorporated evidence into model at ACM1

Table: Key assumptions and evidence sources in company's base case model

Input	Assumption and evidence source
Baseline inputs	Clarity AD
SoC efficacy	Clarity AD (up to 18 months); Potashman et al. (18 months+)
Lecanemab efficacy	Clarity AD (up to 18 months); Potashman et al. with HR from Clarity AD (18 months+)
Mortality	General UK population mortality adjusted by HRs from Crowell et al.
Treatment discontinuation	Constant rate from Clarity AD
Adverse events	Clarity AD
Patient and caregiver utilities	• MCI and mild AD: mixed model for repeated measures using Clarity AD EQ-5D data • Moderate and severe AD: Farina et al. (Black et al. for caregivers) • Disutility from residential care: Farina et al. **Company addendum**
Risk of residential care	Knapp et al. (no risk assumed for MCI subgroup)
Medical costs (primary, community, secondary care)	• Alzheimer's Society 2014 report costs inflated to 2022/23 prices • MCI subgroup costs assumed to be 54% of mild AD costs (Robinson et al.)
Non-medical costs (residential and home-based community care)	• Alzheimer's Society 2014 report costs inflated to 2022/23 prices • MCI subgroup costs assumed to be 54% of mild AD costs (Robinson et al.) but assumed the same for residential care costs

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; HR, hazard ratio; SoC, standard of care

Committee requests at ACM1 (all have been addressed)

Clinical effectiveness	• Distribution of change from baseline in CDR-SB score at 18 months, compared for lecanemab and placebo • Mean difference from baseline by treatment arm at 18 months for the 6 individual domains of CDR-SB • Distribution of the CDR-SB treatment effect for different subgroups • Effect of introducing lecanemab on the proportion of people who have MCI or mild dementia
Transition probabilities	• Justification of constant transition probabilities and other approaches explored • Transition probabilities that lead to outcomes and mortality consistent with trial data and clinical expectations • Scenario with model structure where each node only has 2 model transitions, to align with Gidwani et al. 2020
Stopping rule	• How progression stopping rule would be measured, and how often in practice • Justification of how the stopping rule had been included in the modelling
Treatment waning	• Scenarios exploring treatment waning for people who stop treatment because of all-cause discontinuation • Scenarios exploring varying assumptions for the rate of all-cause discontinuation after 18 months
Utility values	• Utility values for each health state for people with AD and their carers, including data source and justification • Considerations of proxy utility values and adaptation by people with Alzheimer's disease • Least-squares mean change from baseline in EQ-5D-5L utility values, by treatment arm, analysed using a mixed effects model with repeated measures • Complete EAG critique of the final approach to model utility and disutility values
Infusion and private care costs	• Information from the company and NHS England that fully estimates infusion costs and alternatives • Information on the proportion of costs that are private in the Alzheimer's Society report, or an alternative estimate of direct non-medical costs
ICERs	• Disaggregated, discounted, undiscounted results for company's and EAG's base cases, by health states

Abbreviations: APOE-4, apolipoprotein E 4; MCI, mild cognitive impairment; MRI, magnetic resonance imaging

Consultation responses

Consultation responses received from:

- Eisai (company)
- NHS England
- 14 people via online web comments
- Patient and professional organisations:
  - Association of British Neurologists
  - Alzheimer’s Society
  - Alzheimer’s Research UK
  - College of Mental Health Pharmacy
  - Faculty of Public Health
  - Royal College of Psychiatrists

Abbreviations: AD, Alzheimer's disease

Consultation responses – new evidence

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 – NHS England

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

Key issue: Clinical significance of treatment effect (1)

Committee requested detailed CDR-SB results to assess heterogeneity

Figure: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months, by threshold CDR-SB score

Table: Adjusted mean difference vs placebo in CDR-SB by domain

Domain	Change
Memory	[redacted]
Orientation	[redacted]
Problem solving	[redacted]
Community	[redacted]
Home and hobbies	[redacted]
Personal care	[redacted]
Overall	**-0.579 (-33.5%, p<0.00001)**

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MCI, mild cognitive impairment; RR, relative risk difference from placebo

Key issue: Clinical significance of treatment effect (2)

Committee requested detailed change from baseline in EQ-5D-5L, by arm

Table: Adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM

Sub-category		Lecanemab (N=723)	Placebo (N=743)
Patient reported	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
Patient-by-proxy	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
Study partner	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	

NICE

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MCI, mild cognitive impairment

Key issue: Trial generalisability

Committee wanted to know any future changes to the population mix

Committee at ACM1

- Clarity AD is generalisable to UK clinical practice, but would like to see estimates from clinical experts on what the introduction of lecanemab would do to the number of people who are diagnosed with MCI or mild AD

Company

- Consulted 3 clinical experts who agreed that the baseline Clarity AD split of people with MCI and mild AD was generalisable to UK clinical practice, but in the long-term following the introduction of lecanemab
- All clinical experts expected the proportion with MCI would increase over time due to knowledge of and access to treatment for early AD, but the initial proportion would reflect the EAG base case
- Company base case updated to use the EAG's estimates of the baseline distribution of patients across health states (MCI = 38.3%, mild AD = 61.7%)

Alzheimer's Society:

- People with dementia: 50% have mild dementia, 37% moderate dementia, 13% severe dementia
- (Do not share estimates of people with MCI due to AD)

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MCI, mild cognitive impairment

Key issue: Treatment effects by subgroup

Committee requested detailed CDR-SB results by subgroup to assess heterogeneity

Population		Proportion of people that progress to threshold CDR-SB score						
		< 0.5	≥ 0.5	≥ 1	≥ 1.5	≥ 2	≥ 2.5	≥ 3
Age < 65 years	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 65 to 75 years	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥ 75 years	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APOE-4 non-carriers	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APOE-4 heterozygotes	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indicated population	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Abbreviations: APOE-4, apolipoprotein E 4; CDR-SB, Clinical Dementia Rating scale Sum of Boxes

Key Issue: Transition probabilities and model validity

Comparison of health state occupancy in Clarity AD and company model

Figure: Lecanemab health state occupancy, Clarity AD vs. model

Figure: SoC health state occupancy, Clarity AD vs. model

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

Key Issue: Utility values

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

Key Issue: Removing non-reference case costs

Difference in private care costs estimated by the company and EAG

Committee at ACM1

- Unable to determine a preferred proportion of costs that are private and should be removed, asked for info

Company

- Maintain original base case that direct non-medical costs from Alzheimer's Society 2014 report do not include private care costs (no adjustment to account for costs outside of NHS and personal social services perspective)
- EAG estimate (that 63% of costs are private) includes societal costs which is inappropriate, but company uses this figure to estimate the proportion of non-medical costs borne privately
- Company calculations lead to a scenario where the non-medical health state costs are reduced by 47.2%

Alzheimer's Society:

- UK social care costs paid by people with dementia and families is £8.8 billion, 51% of social care total cost
- 63% of £42 billion dementia costs borne by people with dementia and families, mostly paid and unpaid care

EAG comments

- Agree with company scenario analysis that reduces costs from 2014 report by 47.2%, adopts in EAG base case

Abbreviations: IV, intravenous; NHSE, NHS England; NTPS, national tariff payment system

How should private care costs be included?

Managed access (4)

Managed access team feasibility assessment

Key issues	Likelihood data could resolve uncertainty	Comments and questions to committee and experts
Comparators	LOW	Data collection is not proposed to resolve uncertainty here
Trial generalisability	LOW	Data collection is not proposed to resolve uncertainty here
Clinical effects by subgroup	LOW	Data collection is not proposed to resolve uncertainty here
Transition probabilities	LOW	Data collection is not proposed to resolve uncertainty here
Costs: infusion and private care	LOW	Data collection is not proposed to resolve uncertainty here, though some information may be available from other sources
Costs: amyloid beta testing	LOW	Data collection is not proposed to resolve uncertainty here
Utility values	LOW	Data collection is not proposed to resolve uncertainty here

Disaggregated results

Setting	Health state	Discounted			Undiscounted		
		SoC	Lecanemab	Incremental vs. SoC	SoC	Lecanemab	Incremental vs. SoC
QALYs							
Community	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Institution	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life years							
Community	MCI due to AD	-	-	-	[redacted]	[redacted]	[redacted]
	Mild AD	-	-	-	[redacted]	[redacted]	[redacted]
	Moderate AD	-	-	-	[redacted]	[redacted]	[redacted]
	Severe AD	-	-	-	[redacted]	[redacted]	[redacted]
Institution	MCI due to AD	-	-	-	[redacted]	[redacted]	[redacted]
	Mild AD	-	-	-	[redacted]	[redacted]	[redacted]
	Moderate AD	-	-	-	[redacted]	[redacted]	[redacted]
	Severe AD	-	-	-	[redacted]	[redacted]	[redacted]
Costs							
Community	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Institution	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]