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

For public – confidential information is redacted ([redacted])

Technology appraisal committee D [9 May 2024]

Chair: Dr Megan John

Lead team: David Meads, Andy Fox, Carole Pitkeathley

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 key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ 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

NICE

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

Patient perspectives (1)

Alzheimer's is life-limiting for patients and carers

Submissions from Alzheimer's Society, Alzheimer's Research UK, Dementia UK

- Alzheimer's disease is progressive and life-limiting and there is no cure
- For many, a diagnosis instils fear and confusion, impacting the individual with the diagnosis and those involved in their care, as well as their broader family and friends
- Easy for family carers to become socially isolated as they put their own lives on hold, often experiencing a severe deterioration in their own health and wellbeing
- 39% of carers provide over 100+ hours of care a week, 112,540 working age carers no longer in paid work, 147,000+ working less due to caring
- Most cited advantage of lecanemab was slowing the progression of disease
- Experience of lecanemab suggests it works best when used as early as possible
- Concerns with lecanemab include difficulties during infusion, medical equipment and staff expertise, experiences with MRI and PET scans, safety and effectiveness

"'When you've met one person with Alzheimer's disease, you've met one person with Alzheimer's disease'…reflects the risk of making general assumptions on what it's like to live with the disease"

"(a potential treatment)… for me that is like the first potential treatment of cancer, you know it's a start. For such a cruel disease to have some hope…"

Abbreviations: MRI, Magnetic resonance imaging; PET, positron emission tomography

Patient perspectives (2)

Lecanemab offers hope for patients and carers, but must be an informed decision

Direct quotes from patients and carers

"makes me incredibly sad…trying to remember the last time I went out on my own, anywhere"

"You go from being a very confident person, working, to someone who you don't recognise in yourself"

"I found it very hard to come to terms with the fact that I was now a full-time carer…I feel stressed every waking minute"

"struggling to get my wife, in pain, partially incontinent, out of bed and to the toilet I feel desperate, utterly shattered and alone"

"The advantage of lecanemab…is that it holds back the symptoms and is giving me more time to enjoy my life"

"As long as everyone is fully informed of the advantages along with any disadvantages and can make an informed decision, I can't see any argument [against]"

"If you had another six months with more clarity, more purpose for them, more purpose for you, how amazing would that be?"

"he has been falling much faster since [lecanemab] was withdrawn…he would have declined much quicker had he not been on the drug"

Clinical perspectives

Lecanemab addresses significant unmet need but there are challenges

Submissions from FPH, ABN, RCP, NHSE

- AD is a progressive disease with underlying pathology that starts at least 10 years before symptoms, it is complex, and our understanding is incomplete
- Current treatments for AD are limited, leading to small, symptomatic benefits for some patients, but do not target specific aspects of AD
- Meaningful treatments in early AD would prevent or significantly delay progression
- Lecanemab could represent a clear shift in managing dementia, leading to a range of benefits, but there are potential significant challenges:
  - Access to and use of biomarkers, including diagnostic accuracy concerns
  - Variations in diagnostic terminology (6+ ways to describe the same people)
  - System readiness: lack of commissioned care pathways, staff training and expertise, limited capacity and infrastructure, increased costs
  - NHSE: need for substantial staffing, training and infrastructure investment

"For people with…MCI…there are no biological treatments available (symptomatic or disease modifying)…people diagnosed in the NHS…are usually discharged from memory clinics back to primary care, with the advice to be re-referred if their symptoms progress (which…is inevitable)"

Abbreviations: ABN, Association of British Neurologists; AD, Alzheimer's disease; FPH, Faculty of Public Health; MCI, mild cognitive impairment; NHS, NHS England; RCP, Royal College of Psychiatrists

Equality considerations

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 excluding them
- Some ethnic groups were under-represented in trial

Abbreviations: AD, Alzheimer's disease

Key issues for committee discussion

	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

NICE **Company addendum**

Company provided an addendum to submission in April 2024.
EAG has responded but not been able to fully critique these analyses.
Information from the addendum has this label.

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

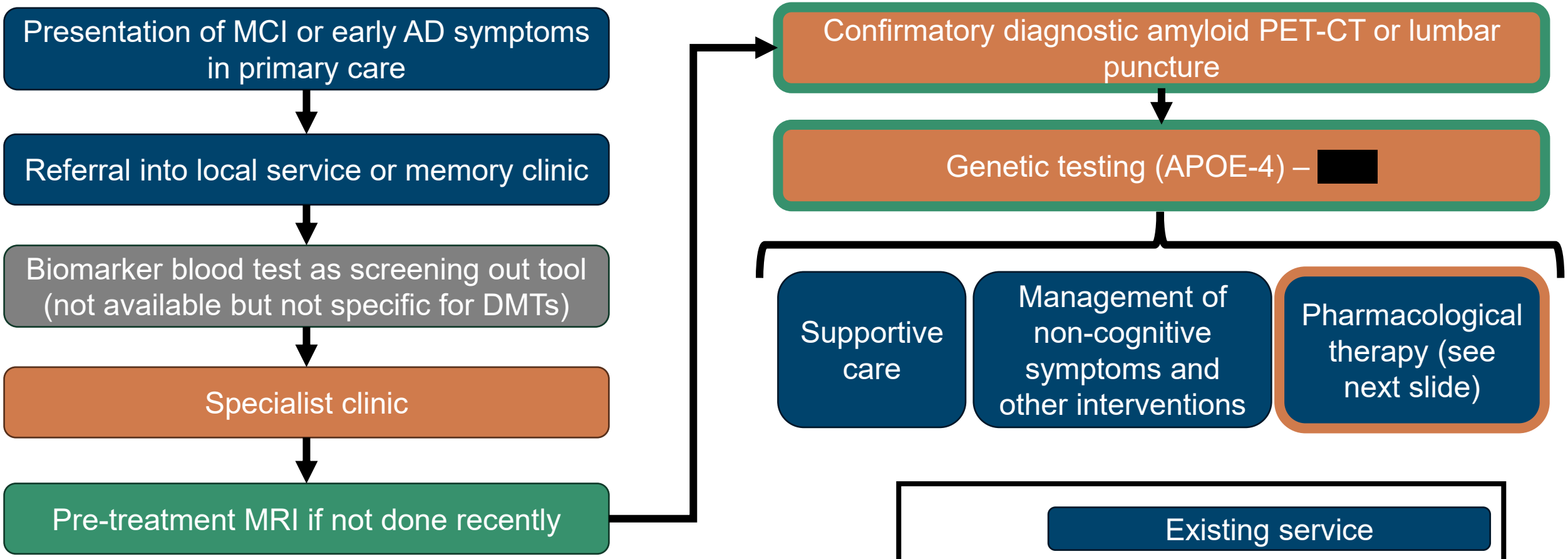
Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

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

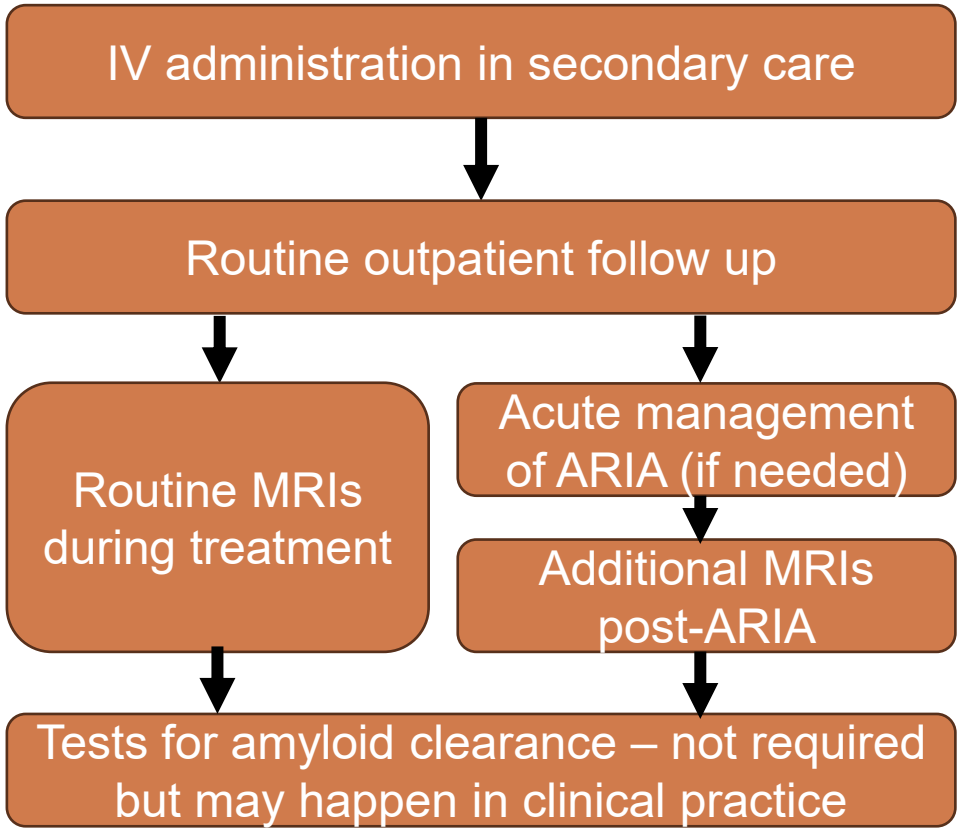
Mild AD

- 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

Lecanemab (Leqembi, Eisai)

Anticipated marketing authorisation	• Not yet been granted marketing authorisation by the MHRA • Anticipated indication wording is: [redacted]
Mechanism of action	• Accumulation of amyloid-beta (Aβ) plaques and tau tangles are characteristic of AD • Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against Aβ marking it for clearance via the immune system • It may also slow down the spread of tau in different areas of the brain
Administration	• Recommended dose of 10 mg/kg, administered as an IV infusion once every 2 weeks • [redacted]
Price	• Proposed list price: [redacted] for 200 mg powder for concentrate for solution for infusion; [redacted] for 500 mg powder for concentrate for solution for infusion • Average monthly cost of [redacted] (based on Clarity AD European patients) • A patient access scheme discount is available

Abbreviations: AD, Alzheimer's disease

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 characterize 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 expected to be released later in 2024

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

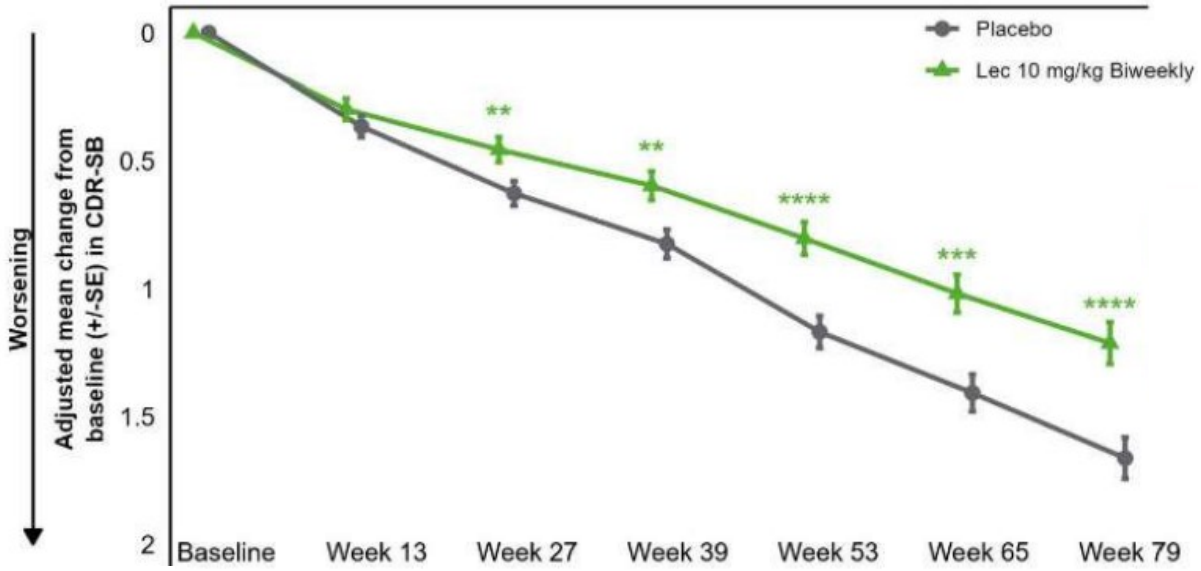
Key clinical trial results

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

Unknown ICER impact

Key issue: Clinical significance of treatment effect

Uncertain whether lecanemab provides a clinically meaningful change

Company

- Lecanemab has shown statistically significant and clinically meaningful slowing of decline (adjusted mean difference of -0.451 in CDR-SB), based on literature and guidance from regulatory authorities
- Outcomes are established, validated, and globally accepted endpoints
- 18-month interval is a short time and full benefits of lecanemab may not be apparent for years
- Delayed start analysis shows 16% slower decline in lecanemab group versus delayed start group (placebo group that switched to lecanemab after 18 months)→ supports the disease modifying effect of lecanemab

EAG comments

- Studies indicate that increase of 1 to 2 points on CDR-SB would be considered a clinically significant decline
- EMA comments from Eisai *Data on file*: "[redacted]"
- EAG clinical expert: "absolute difference of 0.45 on CDR-SB is about the same as achieved by existing anticholinesterase drugs for AD and most people now believe their benefit is clinically meaningful"

Does lecanemab provide a clinically meaningful benefit for people with MCI and mild AD?

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

Unknown ICER impact

Key issue: Comparators

Some treatments in Clarity AD are not licensed or used in NHS clinical practice

Source	MCI subgroup treatments	Mild AD subgroup treatments
NICE scope	Non-pharmacological management	AChEi plus non-pharmacological management
Company (Garcia et al.)	31% receive AChEis, 8% receive memantine	Up to 89% receive AChEis, 7-21% receive memantine
EAG expert	Minority have AChEis, none have memantine	70% have AChEis, 5% have memantine
Clarity AD (see appendix)	**Lecanemab:** [redacted] had AChEi, [redacted] had memantine	**Lecanemab:** [redacted] had AChEi, [redacted] had memantine

MCI	Adjusted mean difference (CDR-SB)	Mild AD	Adjusted mean difference (CDR-SB)
All-comers	-0.35 (28% slowing of decline)	All-comers	-0.62 (27% slowing of decline)
Exc. use of AChEis and/or memantine	[redacted] ([redacted]% slowing of decline, [redacted])	Exc. use of memantine	[redacted] ([redacted]% slowing of decline, [redacted])

EAG comments

- Lecanemab treatment effect appears consistent for whole mild AD subgroup, unclear for MCI subgroup
- Also, effects of concomitant treatment on estimates of lecanemab treatment effect are unclear
- Results need to be interpreted with caution due to the small sample size and lack of statistical power

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

Is SoC in Clarity AD generalisable to NHS clinical practice?

Unknown ICER impact

Key issue: Trial generalisability

EAG questions how relatable the trial is to UK clinical practice

Company

- Clarity AD included 8 UK sites (n=48), baseline characteristics considered generalisable to NHS by UK experts
- Intervention, comparators and outcomes used in Clarity AD are also relevant for the UK context

EAG concerns with trial generalisability

- Clarity AD had 62% MCI: 38% mild AD split, but EAG expert says in UK, likely split is 38% MCI: 62% mild AD
- MCI subgroup comparators in trial not aligned with UK, CDR-SB not used in UK clinical practice

Clinical experts

- Diagnostic pathway used in trial is not widely used in UK, despite many aspects being recommended for use
- Functional unblinding: common infusion reactions (26.4% for lecanemab, 7.4% for placebo), lower rate of completing treatment (84.4% for placebo vs. 81.2% for lecanemab) may impact interview-based outcomes
- People in trial were younger, less diverse, fewer co-neuropathologies (e.g. vascular disease), fewer co-morbidities than UK, may be expected to experience lower treatment effectiveness in clinical practice
- Primary trial outcomes are considered standard in the field, but are better suited to dementia phase rather than MCI phase where the outcome measures are not designed to pick up much smaller and slower rates of change

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

Is the Clarity AD trial data generalisable to the UK?

Large ICER impact

Key issue: Treatment effects by subgroup

EAG suggests treatment effect may vary by age and APOE-4 carrier status

APOE-4 carrier status	Adjusted mean difference (CDR-SB)
Non-carriers (n=542)	-0.75 (41% slowing of decline)
Heterozygote (1 copy, n=924)	-0.50 (30% slowing of decline)
Homozygote (2 copies, n=268)	0.28 (22% faster decline, confidence interval crosses 0)

Age	Adjusted mean difference (CDR-SB)
≥ 75 years (n=641)	-0.72 (40% slowing of decline)
65-74 years (n=749)	-0.37 (23% slowing of decline)
< 65 years (n=344)	-0.08 (6% slowing of decline, confidence interval crosses 0)

Company

- Variability in results and statistical significance expected for subgroups with smaller patient numbers
- [redacted]
- [redacted]
- [redacted]

Does lecanemab have clinically meaningful treatment effect in people who are:
- APOE-4 homozygous? - Below 65 years of age?

Abbreviations: ADCOMS, Alzheimer's disease composite score; ApoE4, apolipoprotein E 4; CDR-SB, Clinical Dementia Rating scale Sum of Boxes

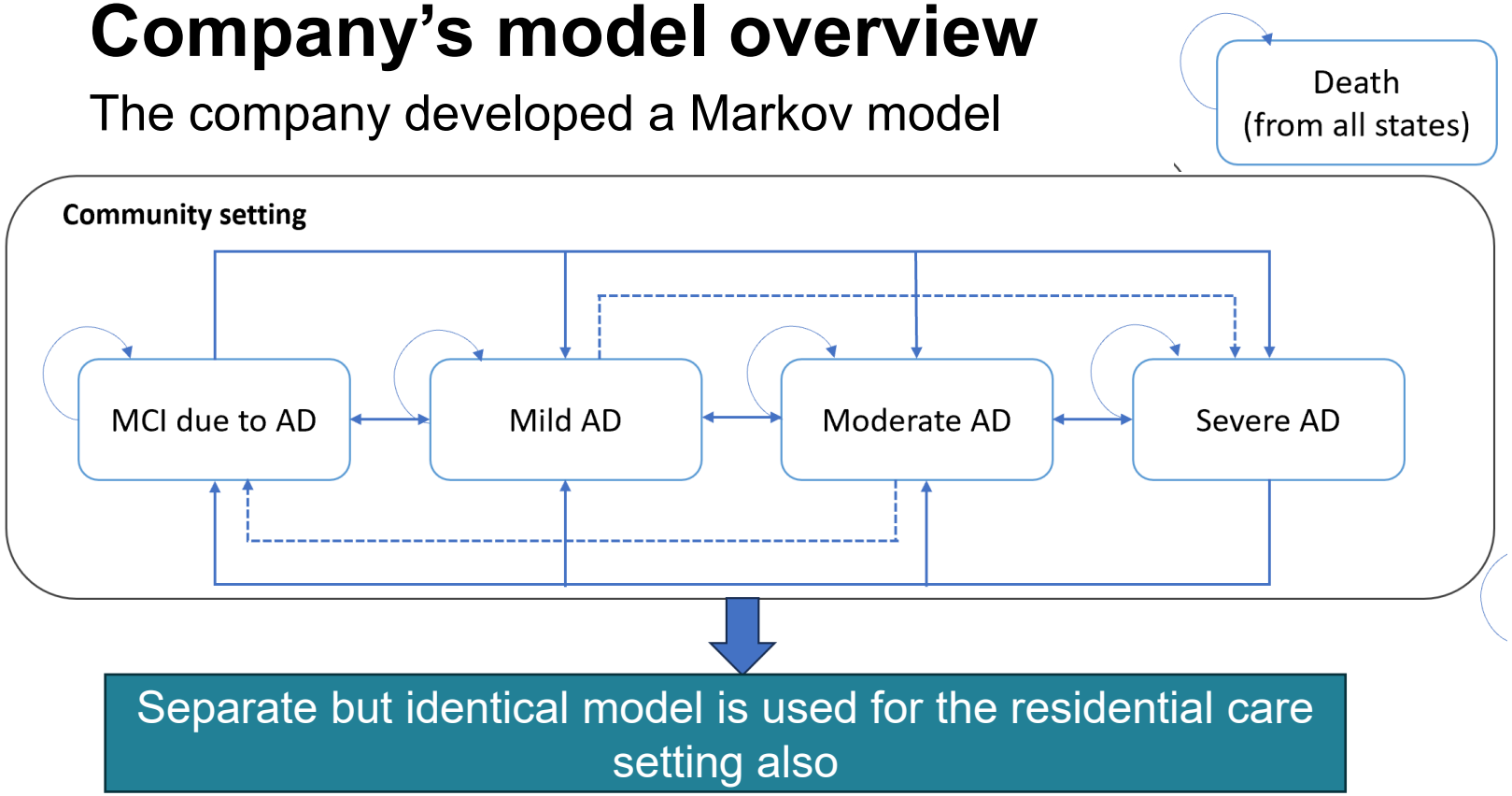
Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

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; MCI, mild cognitive impairment

How company incorporated evidence into model

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

Key Issue: Transition probabilities (1)

Large ICER impact

EAG notes several uncertainties with company's transition probabilities

	Company approach	EAG comments
Backward transitions	Transitions from more severe to less severe health states included in model, consistent with literature, justified due to short cycle length and expert opinion that transitions are temporary	Uncertain if clinically appropriate to include backward transitions → scenario analysis excluding backward transitions increases ICER substantially
Constant transition probabilities	Overfitting trial data → transitions misaligned with underlying risk → used NACC data and constant transition probabilities after 18 months in model performed extensive analyses to explore suitability	Constant transitions at odds with observed increase in transitions from MCI to mild AD, mild to moderate AD, and mild to MCI over time → changes assumption in scenario analysis
Best practice	Gidwani et al. tutorials not used as they led to negative transition probabilities or could not be implemented due to severely limiting structural assumptions (e.g. each node only has 2 model transitions) at odds with natural history	Large discrepancy between company's base case transitions and multistate survival approach, suggests original transitions may not be appropriate – suggest exploring further

See next slide

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Center

Large ICER impact

Key Issue: Transition probabilities (2)

Health state occupancy in the model is not aligned with Clarity AD data

Company

- Model accurately predicts state occupancy in Clarity AD for both arms
- Minor differences may be due to use of life tables with AD mortality estimates
- State occupancy overestimated in severe AD health state for both arms
- But differences are small and consistent between Clarity AD and the model

		Health state occupancy at 18 months (%)				
		MCI	Mild	Moderate	Severe	Death
Lecanemab	Clarity AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	Clarity AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (lecanemab vs. SoC)	Clarity AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in difference (Model vs. Clarity AD)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Differences not considered minor by EAG, clear the model systematically overestimates lecanemab benefits compared with Clarity AD in terms of moderate AD, severe AD and death health state occupancy
- Absolute outcomes are as important as incremental outcomes, there is potential bias favouring lecanemab
- Company's model does not accurately predict health state occupancy as observed in Clarity AD for both arms

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

NICE

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

Key Issue: Estimating long term outcomes

Large ICER impact

18 months treatment-effect in Clarity AD used to estimate long-term outcomes

Company

- Transitions estimated using Clarity AD and literature →
- Lecanemab treatment effect assumed constant for people on treatment and for those who discontinue due to all-cause discontinuation in MCI and mild AD states

Transitions data	0 to 18 months	18 months +
SoC arm	Clarity AD	Potashman et al.
Lecanemab arm (on- and off-treatment)	Clarity AD	[redacted] HR applied to SoC transitions

Company addendum

- Approach justified because HRs were estimated for the ITT population, so discontinuations are captured already
- Assume no treatment waning on treatment and [redacted] waning at treatment discontinuation due to progression

EAG comments

- 18-months follow-up is unlikely long enough to assess treatment effects, 24-month data are still insufficient
- Treatment discontinuation linked mostly to disease progression, so modelled mean treatment time: [redacted]
- Using 18-month outcomes to model long term treatment effect is uncertain, suggest presenting waning scenarios
- Assuming treatment effect for people off-treatment potentially add substantial bias, changed in EAG base case

Clinical experts

- Currently very limited data about whether lecanemab has longer term cumulative benefits after 18 months

How should lecanemab long-term treatment effect be modelled? Is it appropriate to assume the same treatment effect for people on- and off-treatment in the MCI and mild AD health states?

NICE

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

Large ICER impact

Key Issue: Treatment discontinuation (1)

Uncertain how often and when people stop lecanemab treatment

Company

- All-cause discontinuation in Clarity AD was constant, so was modelled at a constant rate: [redacted] for lecanemab
- No treatment stopping rule for lecanemab in trial, but following rules were modelled based on UK expert opinion:
  - Progression to moderate AD: [redacted]
  - Residential care: stop treatment when patient enters residential care

EAG comments

- Unclear if appropriate to use constant trial discontinuation rate beyond 18 months, as in company base case which leads to a modelled mean time-on-treatment of 3.15 years
- Potential double-counting of all-cause discontinuation when combined with stopping rules
- EAG base case removes the severity-based stopping rule as the trial did not use it, EAG clinical expert claims it will be hard to use in practice due to limited use of CDR-SB, and to avoid double-counting
- Removed residential care stopping rule in a scenario based on EAG clinical expert opinion, but uncertain

Clinical experts

- Treatment likely stopped due to adverse events or when treatment is no longer beneficial (e.g., progression)
- Treatment could stop when amyloid negative, but requires ongoing testing even when off-treatment

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

Key Issue: Treatment discontinuation (2)

Large ICER impact

Company addendum

The company provided an [redacted]

Company

- Scenario analysis presented which assumes that [redacted]
- Amyloid PET reduced from 77.9 CL at baseline to [redacted] CL in lecanemab arm at 18 months (end of Clarity AD)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

EAG comments (not had time to fully critique the [redacted])

- [redacted]
- [redacted]

How should treatment discontinuation be included in the model?

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

Large ICER impact

Key Issue: Costs: infusion and private care costs

Difference in costs estimated by the company, NHS England and EAG

Background

- NHSE submitted a cost model that includes some costs that are different from the company's model
- Differences that lead to moderate or large ICER impacts are shown below, others are in the appendix
- Company scenario using NHSE costs means [redacted] driven by £565 IV admin cost

Table: Differences in costs in company, EAG and NHS England models with moderate or large ICER impacts

	Company model	NHS England model	EAG base case	ICER impact
IV infusion	• £207 • 2021/22 NTPS (SB12Z Simple parenteral chemotherapy at first attendance, cost uplifted)	• £565 • 2019/20 NTPS (WD02Z Alzheimer's Disease or Dementia, cost uplifted)	• Align with NHSE	**Large** (EAG addendum)
Private care costs	• Direct non-medical costs from Alzheimer's Society 2014 report • Unclear how much is paid for privately → assume 10% in scenario analysis (so 10% of these costs excluded from model)	• Direct non-medical costs not included	• Other report states two-thirds of costs paid by patients and families as unpaid or private care • Assume two-thirds of costs are paid privately in scenario (so 66% of costs excluded), likely too high	**Moderate** (EAG scenario)

Private care costs are outside of the NHS and personal social services perspective as stipulated by the NICE methods manual

How should infusion and private care costs be included in the model?

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

Key Issue: Costs: amyloid beta testing

Small ICER impact

EAG uses increased amyloid beta testing costs and highlights possible test harms

Company

- Lecanemab treatment is conditional on Aβ pathology so diagnostic testing costs are included in base case
- Assume 90% of tests will be via CSF (lumbar puncture), 10% via PET-CT based on UK expert opinion
- Addendum: Updated base case includes testing costs for people who are tested but ultimately do not receive lecanemab – done by adopting a screening failure rate of 28.8% from Clarity AD trial data

NHSE comments

- Assume 85% of tests will be via CSF (lumbar puncture), 15% via PET-CT based on clinical feedback

EAG comments

- Align with company on testing ratio of 90%:10% for CSF:PET-CT as EAG expert agreed
- Uses higher screening failure rate from the NICE HTA lab report (43.1%)
- Note that model does not capture any potential harm to the health of those tested
- **NICE guideline NG97 on dementia:** "potentially stressful and unpleasant diagnostic tests that could be used…include lumbar puncture to obtain cerebrospinal fluid (CSF) for biomarker tests, MRI and other imaging tests. These tests may not be well tolerated by all patients, particularly those with claustrophobia (MRI) or people with more severe dementia"

Abbreviations: CSF, cerebral spinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography–computed tomograph

How should amyloid beta testing costs be included in the model?

Key Issue: Utility values

Large ICER impact

Company addendum

EAG notes several uncertainties with utility and disutility values

	Company approach	EAG comments	ICER impact
Utilities	Addendum: used EAG suggested MMRM with backward elimination approach, also used proxy utilities due to counterintuitive results	Diagnostics and exact calculations were not provided so EAG cannot critique, uncertainty with using proxy utility values	Not provided
	Treatment dependent health state utilities used	No clear rationale, so use treatment-independent values in base case	**Moderate**
	Utilities not capped at UK population values as they align with literature	Utility values for some states are higher than UK matched population	**Large**
Disutilities	0.09 disutility for caregivers when patient in residential care (i.e. worse utility)	No additional disutility on residential care → impact of residential care unclear	**Moderate**
	Some AE disutilities included in base case in addendum and further scenarios	AE disutilities may be under-estimated, should add disutilities for grade 1/2 ARIA	**Small**

Table: Health state utilities (community setting) – MMRM (addendum)

Treatment	MCI	Mild AD	Moderate AD	Severe AD
SoC	[redacted]	[redacted]	0.674	0.574
Lecanemab	[redacted]	[redacted]	0.686	0.586

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

Abbreviations: AE, adverse event; MMRM, mixed model for repeated measures

Summary of company and EAG base case assumptions

Differences between company and EAG base cases

Assumption	Company base case	EAG base case
Long-term outcomes	Assume long-term treatment effect for people off-treatment in MCI and mild AD groups	Assume no long-term treatment effect for people off-treatment in MCI and mild AD groups
Stopping rule	Include severity-based stopping rule	Exclude severity-based stopping rule
Costs and resource use	Various costs and resource use	Use NHSE estimates
Diagnostic testing costs	Amyloid testing costs for all people tested, using a 28.8% screening failure rate	Amyloid testing costs for all people tested, using a 43.1% screening failure rate
Utility values	Use treatment-dependent utility values	Use treatment-independent utility values
Caregiver disutility	Include caregiver residential care disutility	Exclude caregiver residential care disutility
Patient baseline distribution	MCI: 78.8%; mild AD: 21.2%	MCI: 38%; mild AD: 62%

Abbreviations: AD, Alzheimer's disease; HR, hazard ratio; MCI, mild cognitive impairment; NHSE, NHS England

Cost-effectiveness results

NICE National Institute for Health and Care Excellence

Cost-effectiveness results: company base case

Company addendum

Table: Company base case (deterministic, PAS price)

Technology	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table: Company base case (probabilistic, PAS price)

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

EAG: company's updated model contains major structural changes not detailed in addendum – may affect results. Changes could not be verified in the time available. All company results thus must be interpreted with caution.
Note: the company has since clarified the major structural changes relate to a scenario they were exploring but did not implement and should not affect the results - an updated model with this removed will be provided.

 Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Cost-effectiveness results: company scenarios

Company addendum

Table: Company scenario analyses (PAS price)

Scenario	Deterministic PAS ICER	Probabilistic PAS ICER
Company base case	[redacted]	[redacted]
Diagnostic testing costs excluded	[redacted]	[redacted]
Unpaid care costs: Included	[redacted]	[redacted]
Unpaid care costs: Included for mild moderate and severe AD, excluded for MCI	[redacted]	[redacted]
Caregiver (dis)utility approach: patient and caregiver additive	[redacted]	[redacted]
Cap utilities at general population age and gender norms	[redacted]	[redacted]
Align unit costs with NHSE AD MCI model	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Exclude AE disutilities	[redacted]	[redacted]
Inclusion of APOE4 testing for proportion of patients	[redacted]	[redacted]
Health state utilities for MCI and mild, patient and caregiver – MMRM patient reported	[redacted]	[redacted]
Health state utilities for MCI and mild, patient and caregiver – mean utilities	[redacted]	[redacted]
Inclusion of amyloid beta testing costs only for those treated with lecanemab	[redacted]	[redacted]

[redacted]

Abbreviations: AD, Alzheimer's disease; APOE-4, apolipoprotein E 4; MCI, mild cognitive impairment

Cost-effectiveness results: EAG base case

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

	Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company base case	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCI/mild AD 38%/62%	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment mild/MCI = SoC TPs	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disable severity stopping rule	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality in MCI set HR=1	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-independent utility	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disable caregiver residential disutility	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NHS cost model changes*	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnostic costs for all tested	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company base case before addendum

*Breakdown of itemised costs on next slide

Abbreviations: MCI, mild cognitive impairment; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Cost-effectiveness results: EAG scenario analyses

EAG unable to [redacted] given th time constraints

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

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base case	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disable all-cause tx discontinuation after trial	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Above + enable severity-based stopping rule	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disable residential care stopping rule	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Backward transitions disabled	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use pessimistic imputation (missing = moderate) for transitions	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multistate survival transition probabilities	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality estimates from Potashman et al	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cap utility at general population values	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume 2/3 of direct non-medical are private costs	Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost-effectiveness results: EAG scenario – NHSE costs

Table: EAG base case scenario to include NHSE costs (deterministic, PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab administration costs £565 instead of £207.59					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI frequency increased					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CSF and test scan cost increased					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company base case before addendum

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Aspects not captured in modelling

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

Uncertainties from the company:

- Long-term clinical effectiveness
- Lecanemab compliance
- Discontinuation and time on treatment
- Baseline patient characteristics

Data collection concerns:

- Collection of real-world NHS data due to limitations in required specialist resources, infrastructure and equipment
- Not aware of infrastructure or registries in NHS for collecting AD patient data

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
- 6-month follow-up (24 months total) already shared for 646 people
- 12-month follow-up (30 months total) expected in July 2024

Alzheimer's Disease Neuroimaging Initiative (ADNI) database

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

Real-world NHS England clinical data

- NHS England propose pilot sites for phased collection of real-world data
- Blueteq may be used to identify when a patient has lecanemab
- Expected lecanemab population in NHS England:
  Year 1 ([redacted]) → Year 3 ([redacted]) → Year 5 ([redacted])

Abbreviations: AD, Alzheimer's disease

Managed access (2)

Managed access team feasibility assessment

Key issues	Managed access team judgement
Clinical significance of treatment effect	Data collection feasible, but has not yet been proposed
Comparators	No further data collection possible or proposed
Trial generalisability	Data collection feasible, but has not yet been proposed
Clinical effects by subgroup	Data collection feasible, but has not yet been proposed
Transition probabilities	Data collection possible to support resolution of this uncertainty
Estimating long term outcomes	Data collection possible to support resolution of this uncertainty
Treatment discontinuation	Data collection possible to support resolution of this uncertainty
Costs: infusion and private care costs	No further data collection possible or proposed
Costs: amyloid beta testing	No further data collection possible or proposed
Utility values	No further data collection possible or proposed
Starting distribution in model	No further data collection possible or proposed
Costs: tests, MRIs and appointments	No further data collection possible or proposed

Likelihood data collection could sufficiently resolve uncertainty: LOW MEDIUM

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

Managed access (3)

Managed access team notes limited scope for resolving uncertainties

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:

- Most uncertainties are modelling or data choices that the committee need to discuss and conclude upon
- Some uncertainties would have some level of resolution through longer-term data from the clinical trial, or through a carefully designed RWE study – this would require extensive engagement with NHSE
- Limited data collection can be achieved through the clinical trial though it is unclear how long it will be continuing
- Setting up a de novo RWE data collection would likely require significant time and resources, would cause some burden on patients and the system
- Giving access to only a portion of the eligible population is against IMF and managed access principles

Abbreviations: IMF, Innovative Medicines Fund; NHSE, NHS England; RWE, real-world evidence

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

	Issue (EAG report key issue number/s)	ICER impact	Slide
Clinical-effectiveness	Clinical significance of treatment effect (6)	Unknown	15
	Comparators (2, 3)	Unknown	16
	Trial generalisability (7)	Unknown	17
	Clinical effects by subgroup: age and APOE-4 carrier status (4, 8, 10)	Large	18
Cost-effectiveness	Transition probabilities and validity of model outcomes (12, 21)	Large	22
	Estimating long term outcomes (5, 13)	Large	24
	Treatment discontinuation (15)	Large	25
	Costs: infusion and private care costs (19, 20)	Large	27
	Costs: amyloid beta testing (1)	Small	28
	Utility values (16, 17, 18)	Large	29
Appendix	Starting distribution in model (11)	Moderate	51
	Costs: tests, MRIs and appointments (9, 19)	Small	52

Abbreviations: APoE4, apolipoprotein E 4

Key questions for the committee

	Key questions
Clinical-effectiveness	Does lecanemab provide a clinically meaningful benefit for people with MCI and mild AD?
	Is SoC in Clarity AD generalisable to NHS clinical practice?
	Is the Clarity AD trial data generalisable to the UK?
	Does lecanemab have clinically meaningful treatment effect in people who are: - APOE-4 homozygous? - Below 65 years of age?
Cost-effectiveness	Is the company's model appropriate for decision-making?
	How should lecanemab long-term treatment effect be modelled? Is it appropriate to assume the same treatment effect for people on- and off-treatment in the MCI and mild AD health states?
	How should treatment discontinuation be included in the model?
	How should infusion and private care costs be included in the model?
	How should amyloid beta testing costs be included in the model?
	What approach for utility and disutility values should be used in the model?
	Which proportions of people with MCI and mild dementia should be used in the model?
	Which costs and resource use should be included in the model?

NICE National Institute for Health and Care Excellence

Thank you.