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

For onscreen – [redacted]

Second appraisal committee meeting

Technology appraisal committee D [15 January 2025]

Chair: Dr Raju Reddy

External assessment group: Southampton Health Technology Assessments Centre

Technical team: Catherine Spanswick, Victoria Kelly, Ross Dent

Company: Eli Lilly and Co

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

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

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Committee conclusions at 1st committee meeting (ACM1)

Donanemab not recommended
Preferred assumptions:

- Model structure acceptable for decision making

Committee preferred assumptions at ACM1	Adopted by company at ACM2?
EAG's source for annual risk of residential care (GERAS study)	Yes
EAG's values for mortality rate, including assumption that rate increases with severity of Alzheimer's disease	No, but company has updated source for mortality values
EAG's long-term treatment-effect assumptions • but also asked for other scenarios to be explored	No – company has modelled new assumption for waning
EAG's preferred values for patients and carer utilities • but asked for justification of both EAG and company approach	No – approaches unchanged, but further justification provided
APOE4 testing costs should include an outpatient consultant visit	Yes
Remove one-off terminal care cost	Yes
Remove unpaid care costs	No – retained unpaid care costs

- Appendix: Committee conclusions at ACM1 – recommendation and uncertainties identified

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Abbreviations: ACM1, 1st committee meeting; APOE4, apolipoprotein E 4; EAG, evidence assessment group

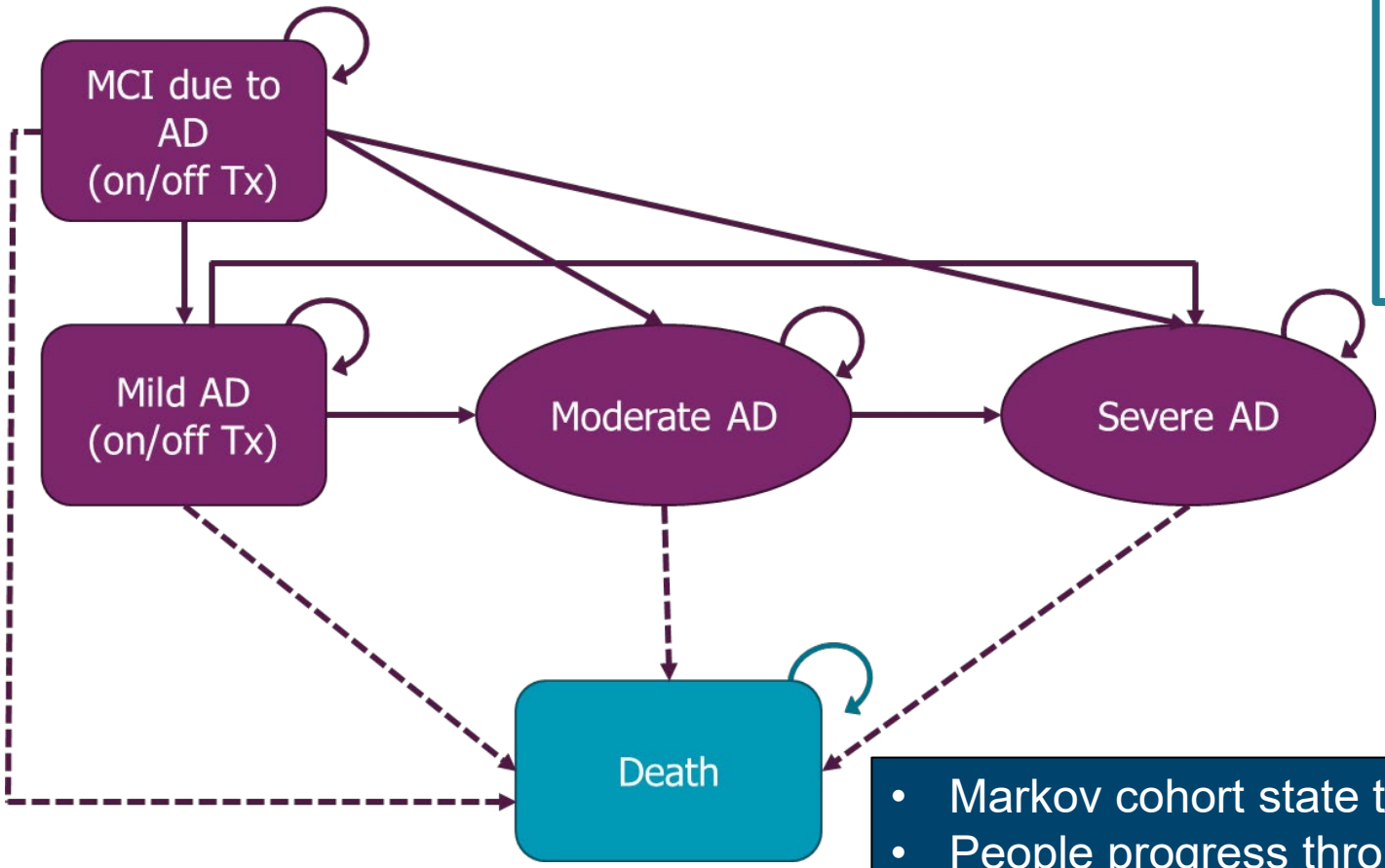
Key issues for committee discussion at 2nd committee meeting

	Issue	ICER impact
Clinical-effectiveness	Modelling clinical effectiveness	Small to moderate
Cost-effectiveness	Hazard ratios for mortality by Alzheimer's disease severity	Large
	Long term treatment effect assumptions	Large
	Patient utilities	Large
	Carer utilities	Large (values)
	Health state occupancy at start of model: new issue	Large
	Costs: company, EAG and NHSE	Moderate (infusion)

Abbreviations: EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; NHSE, NHS England

Company's model overview

The company developed a Markov model



Donanemab (Kisunla, Eli Lilly & Co):

- Marketing authorisation (MA) granted October 2024: For treating: 'mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers'
- First committee meeting held before final MA known, so committee considered full TB-ALZ 2 trial population, including APOE4 homozygotes

Company – updates for 2nd committee meeting include:

- In line with MA, population updated and donanemab is stopped on progression to moderate AD
- Health state occupancy at start of model

- Markov cohort state transition model
- People progress through 4 AD health states based on disease severity
- Single model for community and residential care settings
- Lifetime horizon (28 years)
- 6-month cycle length with half-cycle correction

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; MA, marketing authorisation; MCI, mild cognitive impairment; TB-ALZ 2, TRAILBLAZER-ALZ 2; Tx, treatment

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Summary of consultation responses

- Names of the organisations that submitted and more detailed summaries from each response are provided on additional slides – Appendix: Consultation responses (5 slides)

Detection and diagnosis:

Prevention of Alzheimer's disease is not prioritised

Changes in diagnosing needed to identify Alzheimer's disease early – people may become ineligible for treatment if delayed

Psychological impact of APOE4 testing not captured

Mild cognitive impairment – not correct to state in draft guidance that it always leads to dementia

Donanemab effectiveness:

Trial exclusion criteria were strict and excluded people with Down's syndrome or young-onset Alzheimer's disease

Treatment effect – disagreement about whether clinically meaningful or not

Monitoring of amyloid by PET and potential early treatment stopping unlikely to be achievable (capacity issue)

Donanemab costs:

Infusion cost may be lower than NHSE estimate

Appropriateness of excluding **informal care costs**

Some inconsistencies with NICE appraisal of lecanemab

Concern that **severity modifier was** not applied

Wider picture: timely diagnosis → less use of NHS resources

Managed access would allow for longer term data collection on efficacy and safety, infrastructure development and greater understating of system-level costs

Abbreviations: APOE4, apolipoprotein E 4; NHSE, NHS England; PET, positron emission tomography

Appendix: Consultation responses – NHSE

NHS England consultation response – updated cost assumptions

Likely eligibility for donanemab

- Now assumes 1 in 7 people presenting in primary care with symptoms would ultimately go on to have donanemab (updated from 1 in 6 to exclude APOE4 homozygotes)

Infusion cost

Updated: £432

- Now assumes same as for COVID-19 monoclonal antibody
- Cautions against focus on only 1 element of costing. NHS pricing typically charges based on 'average cost' principle, mostly using published tariffs. Actual resource requirements might differ from average for eligible cohort (standard tariffs)

Consideration of early treatment stopping due to amyloid clearance

2 scenarios

- Previous estimate based on company comment that 15% would have PET scan at 6 or 12 months and stop donanemab if scan showed amyloid clearance. Updated approach incorporates impact of licence:

Scenario 1 – with PET scanning:	Scenario 2 – no PET scanning
15% of patients scanned at 6 months and 17% scanned at 12 months will have amyloid clearance and can stop donanemab, so total 32% stopping treatment early → average treatment duration ~62 weeks	Donanemab given for 18 months with no amyloid monitoring (may overestimate actual duration)
Dependent on NHSE securing sufficient radiotracer supply and PET-CT scanning capacity (which will also be required in diagnosing patients)	No dependency on radiotracer availability or PET-CT capacity
Predicted cost [redacted] per patient*	Predicted cost [redacted] per patient*

*Average cost incorporating updated infusion price and impact of license that excludes APOE4 homozygotes. Does not reflect updated PAS price of donanemab

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; MCI, mild cognitive impairment; NHSE, NHS England; PET-CT, positron emission tomography-computed tomography

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Changes to the company base case for 2nd committee meeting

Assumption	Company updated base case
Population	• Aligns with marketing authorisation: excludes APOE4 homozygotes, patients with missing APOE4 status, and patients having anticoagulants
Stopping rule	• Aligns with marketing authorisation: stop treatment on progression to moderate AD
Transition to residential care	• Accepts EAG preferred source (GERAS study) for annual risk of transitioning to residential care
Mortality	• Applies variable mortality risk across different severity stages of AD, using company-preferred NACC analysis as source of mortality data
Long-term treatment effect and waning	• Duration of full treatment effect extended to 5.5 years (4 years is after stopping) • Duration of treatment effect waning extended to 9 years
Diagnosis and monitoring costs	• Added cost of 1 neurologist outpatient visit for APOE4 testing and 1 neurologist outpatient visit every cycle (6 months) for monitoring (licence and EAG preference)
Health state costs	• Accepts committee preference to not included added terminal care costs
Health states at start of model	• Proportions of patients starting model in MCI and mild AD health states changed

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; EAG, evidence assessment group; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

Clinical effectiveness in indicated population*, from Summary of Product Characteristics (*excludes APOE4 homozygotes)

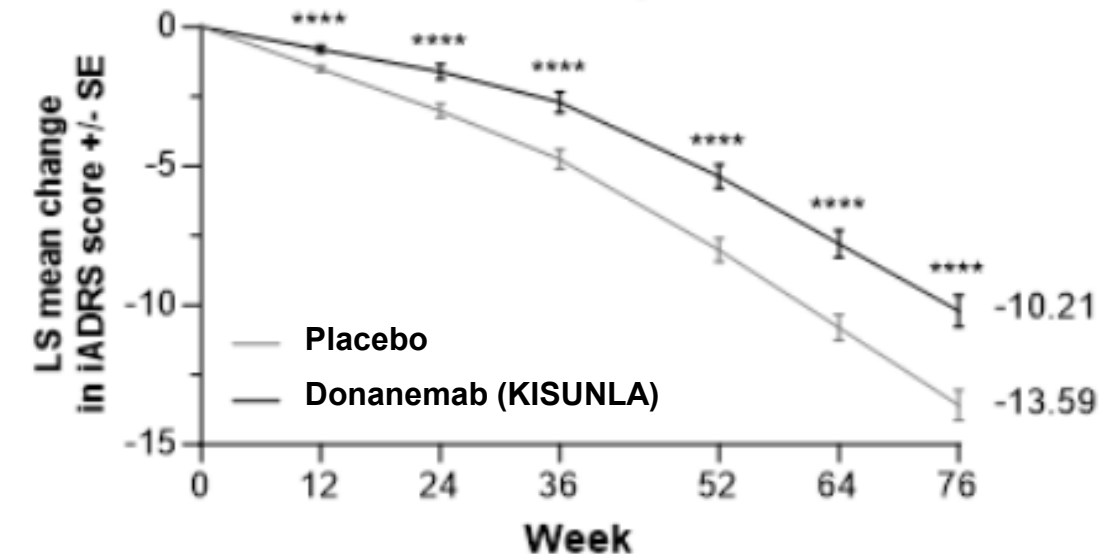
Donanemab reduces decline seen in iADRS and CDR-SB score at 18 months

- Appendix: Background on Alzheimer's disease, Donanemab (Kisunla, Eli Lilly & Co), Key clinical trials

Table: Results of TB-ALZ 2 for indicated population* (N=1447) at 18 months

Treatment arm	Donanemab (n=717)	Placebo (n=730)
iADRS – NCS2 analysis:		
Mean baseline	104.66	103.83
Change from baseline	-10.21	-13.59
Difference from placebo (95% CI) [p-value]	3.38 (1.83 to 4.92) [<0.0001]	
CDR-SB - MMRM analysis:		
Mean baseline	3.96	3.94
Change from baseline	1.67	2.43
Difference from placebo (95% CI) [p-value]	-0.77 (-1.04 to -0.49) [<0.0001]	

Figure: Mean change from baseline in iADRS in TB-ALZ 2 for the indicated population*



Abbreviations: APOE4, apolipoprotein E 4; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; LS, least squares; MMRM: mixed models for repeated measures; NCS2: natural cubic spline with 2 degrees of freedom; TB-ALZ 2, TRAILBLAZER-ALZ 2

Small to moderate ICER impact

Key issue: Modelling clinical effectiveness

Company provided meta-analyses of 2 trials but prefers TB-ALZ 2 for base case

Committee at ACM1

- Acceptable to use CDR-SB in the model but would like the company to explore alternative hazard ratios for disease progression for CDR-SB and iADRS, from a meta-analysis of TB-ALZ 2 and TB-ALZ

Faculty of Public Health comments and College of Mental Health Pharmacy

- Donanemab treatment effect size is not clinically meaningful

Company

- Provided meta-analysis – Appendix: Clinical effectiveness results (UK indicated population)
  - Comparing trial results from NCS2 and MMRM models suggests risk of bias within results is low
- Results of meta-analysis should be interpreted with caution, as design of trials differ:
  - TB-ALZ trial only included patients with low-medium tau
  - some exclusion criteria differ, e.g. historical/existing medical conditions and prior/concomitant therapy
  - different rules for stopping treatment
- Treatment effect used in model remains as CDR-SB from TB-ALZ 2 due to the consistency of the data source, but is updated for UK eligible population

Abbreviations: CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; ICER, incremental cost-effectiveness ratio; MMRM: mixed models for repeated measures; NCS2: natural cubic spline with 2 degrees of freedom; TB-ALZ (2), TRAILBLAZER-ALZ (2)

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Small to moderate ICER impact

Key issue: Modelling clinical effectiveness

Company provided meta-analyses of 2 trials but prefers TB-ALZ 2 for base case

Company

Table: HRs for disease progression (UK eligible population)

Source	Measure	HR (95% CI)	In model?
TB-ALZ 2	CDR-SB	[redacted]	Base case
	iADRS	[redacted]	X
Meta-analysis	CDR-SB	[redacted]	Scenario
	iADRS	[redacted]	X

- Company scenario using CDR-SB result of meta-analysis for treatment effect increased ICER from £12,091 to £14,618

EAG comments

- Unclear how many participants excluded because they would be ineligible
- Company provided simple pooled results not a meta-analysis with weighted pooled estimates and no random effects model to address heterogeneity between trials
- EAG clinical experts agreed that minor differences between trials unlikely to impact outcomes, so EAG prefers to use HR from meta-analysis
- Scenario using TB-ALZ 2 reduces EAG ICER from £135,284 to £124,496/QALY

Faculty of Public Health comments

- Exclusion criteria in trials, and high screening failure rate, are relevant to generalisability of results
- 10-year average age difference between trial cohorts and development of dementia in general population

Which analysis of trial results does the committee prefer to use to inform the model?

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Abbreviations: CDR-SB, Clinical Dementia Rating scale Sum of Boxes; EAG, evidence assessment group; HR, hazard ratio; iADRS, Integrated Alzheimer's Disease Rating Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SmPC, summary of product characteristics; TB-ALZ (2), TRAILBLAZER-ALZ (2)

Large ICER impact

Key issue: Hazard ratios for mortality by AD severity

Company updated base case to incorporate variable mortality risk by AD severity

Committee at ACM1

- Uncertainty about the risk of death across Alzheimer's disease severities
- Preferred EAG's approach which included assumption that risk of death increases as Alzheimer's disease becomes more severe and was based on recent evidence that was most closely aligned with this population.

Company

- Updated base case to use US NACC analysis, which incorporates variable mortality risk by AD severity
- Values align with clinical expert opinion that notable increase in risk of death likely in severe AD dementia
- Lower mortality rate for moderate compared to mild AD dementia in NACC analysis not a true difference since confidence intervals overlap. Differences are captured in probabilistic ICER
- **Population:** EAG's analysis may include non-AD forms of dementia (due to lack of amyloid testing). Non-AD dementia can have higher mortality risk compared to AD so EAG may overestimate mortality in AD
- **Reference group:** Company analysis considers MCI due to AD as reference cohort whereas EAG's source (Crowell et al) uses general population as reference cohort, suggesting these values may be inflated
- **Methodology:** Crowell treats death as a competing event, so HRs represent relative risk of death for each disease stage (survival time within each stage). Company's NACC analysis considers cumulative effect of time spent across different disease stages → more appropriate to how HRs are implemented in model, as applied to general population life tables not to transition probability to death

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; CI, confidence interval; HR hazard ratio; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

Large ICER impact

Key issue: Hazard ratios for mortality by AD severity

Company updated base case to incorporate variable mortality risk by AD severity

EAG comments

- EAG's approach unchanged. Crowell et al. uses same underlying NACC dataset as company's approach. Company's approach limits population to amyloid positive → relevant population

Table: Mortality risk compared with general population

Health state	**EAG base case** (Crowell et al. NACC data)	**Company updated base case** (NACC data)
MCI	1	1
Mild AD (CI)	2.4 (1.68 to 3.33)*	1.79 (1.54 to 2.09)†
Moderate AD (CI)	3.1 (2.44 to 3.94)*	1.75 (1.42 to 2.14)†
Severe AD (CI)	6.6 (4.82 to 9.07)	3.41 (2.87 to 4.07)

*†CIs overlap

EAG notes: Company's values for mortality risk in mild, moderate or severe AD are lower than reported in all publications it identified, while EAG's are between Ross et al. and Lin et al. – Appendix: Hazard ratios

- Better understanding of strengths and limitations of company's NACC analysis necessary to provide sufficient grounds for decision-making
- Crowell analysis only had biomarker data for a small group of participants, so this was not used to confirm AD – may have misclassified both AD and non-AD, especially in MCI as symptoms often less recognisable
- Scenario using company's analysis of NACC increases EAG ICER from £135,284 to £150,893/QALY

Is the company's approach to predicting mortality is suitable for decision making?

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Abbreviations: AD, Alzheimer's disease; CI, confidence interval; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre; QALY, quality-adjusted life year

Large ICER impact

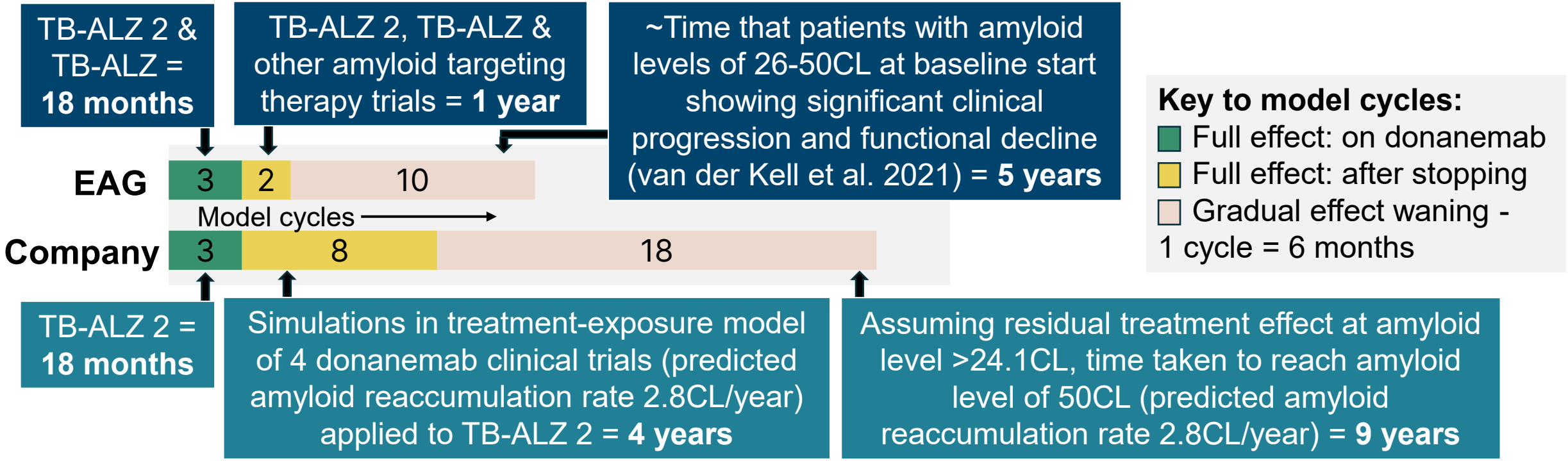
Key issue: Long-term treatment effect assumptions

Company and EAG disagree on modelled treatment effect duration and waning

Committee at ACM1

- Longer-term clinical effects of donanemab unknown. Company's and EAG's modelling highly uncertain
- In the absence of better evidence, preferred EAG's approach, which was based on the limited clinical trial evidence presented, but would like other scenarios to be explored

Figure: Summary of updated company and EAG base case assumptions showing number of cycles assumed for treatment effect and waning and sources of evidence



Abbreviations: CL, centiloids; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; TB-ALZ (2), TRAILBLAZER-ALZ (2)

Large ICER impact

Key issue: Long-term treatment effect assumptions

Company and EAG disagree on modelled treatment effect duration and waning

Company

- Considers EAG approach at 1st committee meeting, assuming all treatment effect is lost once amyloid positivity (>24.1CL) returns, is highly unrealistic. Provided evidence linking defined amyloid plaque level with time to clinical progression (van der Kall et al. 2021, Quenon et al. 2024, Sperling et al. 2024)
- Company's updated approach extends assumed duration of full effect after stopping from 3.5 to 4 years because simulation being applied to licence population of TB-ALZ 2, and extends duration of gradual effect waning from 5 years to 9 years. Explores scenarios of 11, 7, 5 and 3 years waning duration

EAG comments

- Company's assumed amyloid re-accumulation rate (median) is predicted by model simulations informed by data from 4 donanemab clinical trials. Therefore, not informed by long-term evidence, and it is uncertain whether the same linear rate of re-accumulation would be observed in the long-term
- EAG maintains same duration of full effect after stopping, which is based on clinical evidence
- EAG updates waning duration based on evidence that clinical progression and functional decline only occurred after 4-5 years of follow-up in people with amyloid levels between 26-50CL. Note: these data are from cognitively normal people or those with an MMSE 25–30 at baseline so differ from model population
- Scenario applying company's preferred long-term treatment effect assumptions to EAG base case reduces EAG ICER from £135,284 to £92,039/QALY

Are the company's long-term treatment assumptions reasonable? What is the committee's preferred approach?

Abbreviations: CL, centiloids; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MMSE, mini mental state examination; QALY, quality-adjusted life year; TB-ALZ 2, TRAILBLAZER-ALZ 2

Large ICER impact

Key issue: Patient utilities

Company and EAG provide further justification of their approaches (unchanged)

Committee at ACM1

- EAG's values are relevant UK estimates, but would like to see further information from company and EAG on their approaches, justifying use of proxy values

Company

Appendix: Patient utility values

- No change to base case (Landeiro et al meta-analysis)
- EAG's GERAS study was in community setting so may not have captured more severe AD. MMSE definitions higher than expected, so utility in patients with severe AD overestimated – Company's re-analysis in appendix
- **Proxy values:** accepted for Alzheimer's disease TA217
- Not possible to measure HRQoL directly from patients with more severe disease due to cognitive decline.
- Better to use consistent source for all health states
- Literature shows proxy values correlate with MMSE score at different stages of Alzheimer's disease
- Uncertainty explored within probabilistic analyses

EAG comments

- Agrees with use of proxy for patient utilities
- Preferred source unchanged: GERAS study, which provides largest number of patients in Landeiro analysis including UK patients
- GERAS study limitation: only 40% of those moderately severe/severe AD had MMSE <10
- Landeiro analysis not NICE Reference case, it pools EQ-5D scores using different countries' value sets, not clear if generalisable
- Scenario applying company's patient utilities from Landeiro to EAG base case reduces EAG ICER from £135,284 to £102,581/QALY

Are proxy utility values acceptable for decision making? Which estimates are preferred (previously EAG)?

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Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MMSE, mini mental state examination; QALY, quality-adjusted life year

Large ICER impact (values)

Key issue: Caregiver utilities

Company and EAG provide further justification of their approaches (unchanged)

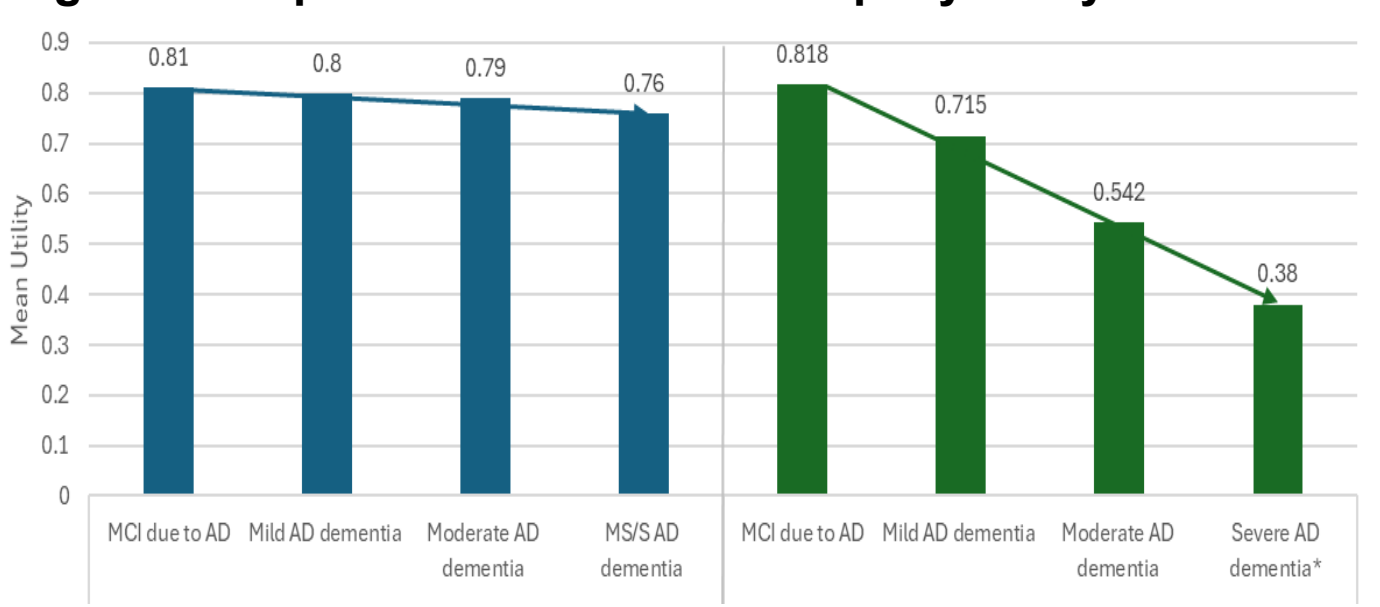
Committee at ACM1

- EAG's approach based on a large study giving UK relevant estimates; 1 carer consistent with this source
- Committee did not have enough information to make a decision about the company's approach to deriving carer utilities. It encouraged the company to justify and explain its approach further

Company – approach unchanged

- 2 vignette studies split by spouse or child caregivers, community or residential setting
- Literature supports that EQ-5D not appropriate for caregivers of patients with MCI or mild AD. Other generic and condition-specific instruments focus on patient health not caregiver impact
- EAG's GERAS values conservative – decline is only 0.04 from mild to severe AD vs. 0.34 decline in company's approach
- Tables of all values used: Appendix: Caregiver utility values

Figure: Comparison of EAG and company utility values



Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment

Large ICER impact (values)

Key issue: Caregiver utilities

Company and EAG provide further justification of their approaches (unchanged)

Company

Appendix: Caregiver utility values

- **Vignette justification:** Caregiver focus groups commonly report: uncertainty whether their loved one understands or remembers, work related impact, loss of time to themselves, irritation and frustration, performing tasks they previously didn't do including driving – has limited overlap with what EQ-5D measures
- **Living arrangement:** Whether carer living or not living with patient had small ICER impact (ACM1)
- **Number of carers:** Disutility impact may be different for secondary carers, but not zero. No change: 1.8 caregivers assumed, sourced from GERAS EU study (N=526 UK cohort). Scenarios: if 1.2 or 1 caregivers assumed, modest increase in company ICER from £12,091 to £14,073/QALY or £14,886/QALY respectively

EAG comments

- **EQ-5D justification:** vignette approach used time trade-off and utilities reported by general population participants, rather than caregivers for patients with Alzheimer's disease. Most aspects relevant to carers not directly health-related. EQ-5D captures mental health impact
- **Carer type and setting:** EAG maintains GERAS as source, which applies same utilities regardless of carer type and setting. Scenarios based on company's vignettes + adjusted GERAS values for (1) carer for parent and residential or (2) residential only reduced EAG ICER from £135,284 to ~£105,000/QALY
- **Number of carers:** Updated to assume 1.2 caregivers (was 1). Scenario applying company's approach for utility values + 1.8 carers to EAG base case reduces EAG ICER from £135,284 to £79,920/QALY

Which estimates are preferred (previously EAG)? How many caregivers should be assumed?

Abbreviations: ACM1, 1st committee meeting; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; ICER incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Large ICER impact

Health state occupancy at start of model: new issue

Company updates model starting health state proportion based on RWE

Company

- Change from TB-ALZ 2 proportions not requested by committee. Company considered update needed because marketing authorisation requires patients to stop treatment once moderate AD dementia reached
- Company's clinical expert suggested that impact of stopping rule is that treatment would more likely be initiated earlier in disease and would be less likely be initiated in later stages of mild AD
- RWE studies of lecanemab use suggest 49% to 79% people starting treatment have MCI (US studies)
- Scenarios using proportions: (a) assumed in lecanemab appraisal (38% MCI, 62% mild AD) increases company ICER from £12,091 to £19,119/QALY; (b) from TB-ALZ 2 increases ICER to £23,786/QALY

Table: Proportion of patients starting the model by health state

Health state at start of model, %	**EAG preferred base case** and Company original base case (TB-ALZ 2)	**Company updated base case** (Kile et al 2024: lecanemab, RWE in USA, N=234)
MCI	20%	70%
Mild AD	80%	30%

EAG comments

- EAG approach unchanged – using TB-ALZ 2 more closely aligned with source of treatment effect, which is different for MCI and mild AD
- Currently unknown what starting proportions could be in NHS practice
- Scenario applying company's updated proportions to EAG base case reduces EAG ICER from £135,284 to £102,807/ QALY

Are the company's assumptions reasonable? Would most people eligible for donanemab start treatment when they have MCI?

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; MCI, mild cognitive impairment; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RWE, real world evidence; TB-ALZ 2, TRAILBLAZER-ALZ 2

Modelled costs: company, EAG and NHSE

Moderate ICER impact (infusion)

Difference in costs estimated by the company and NHS England

Committee at ACM1: Estimates differ between company and NHSE, requested further explanation

Company:

- **Diagnosis:** Now includes costs of neurology outpatient visits for APOE4 diagnostic test and for monitoring (1 per 6-month cycle) – EAG base case. Assumes testing 2 patients (CSF or amyloid PET) identifies 1 eligible
- **Infusion:** NHSE cost represents a considerable overestimation of the administration costs. Scenario applying NHSE administration cost to company base case increases company ICER from £12,091 to £16,151/QALY
- For some combinations of assumptions that include the NHSE infusion cost, donanemab may not be considered cost effective even at very low or zero cost

NHSE: Infusion cost: costing is consistent with lecanemab appraisal

EAG: Infusion cost: Uses revised NHSE cost (£432). Scenario applying company's preferred infusion cost to EAG base case reduces ICER from £135,284 to £120,439/QALY

Eisai (comparator) – based on NHSE model:

- Notes cost of genetic counselling not included (£350), which lecanemab EAG applied to 50% of people testing APOE4 homozygous
- Outpatient visit every 3 months for monitoring

Association of British Neurologists:

- Arguable that molecular testing (CSF or amyloid PET) should not have been included in modelling as ideally it is routinely available to support diagnosis of AD (NG97)

Are the company's cost assumptions for diagnosis reasonable?
Which infusion cost should be used in decision-making?

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Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; CSF, cerebrospinal fluid; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; NG97, NICE guideline 97; NHSE, NHS England; PET, positron emission tomography; QALY, quality-adjusted life year

Summary of company and EAG base case assumptions

Differences between company and EAG base cases

Assumption	Company updated base case	EAG base case
Source for modelling clinical effectiveness	TB-ALZ 2 trial	Meta-analysis of TB-ALZ 2 and TB-ALZ trials
Starting proportion	70% MCI due to AD 30% mild AD	20.4% in MCI due to AD 79.6% in mild AD (from TB-ALZ 2)
Mortality risk for AD	Increases with severity in mild to severe AD; NACC (biomarker population)	Increases with severity in mild to severe AD; Crowell et al. (age 80)
Long-term treatment effect and waning	Full effect for 5.5 years Gradual waning for 9 years	Full effect for 2.5 years Gradual waning for 5 years
Patient utility	Landeiro et al. with EQ-5D using values sets from different countries combined	GERAS study community setting with EQ-5D using UK value set
Caregiver utility (number)	2 vignette studies (1.8 caregivers)	GERAS study (1.2 caregivers)
Healthcare resource use	Wittenberg et al., including unpaid care	Wittenberg et al., unpaid care excluded
Infusion cost	£207.59 (SB12Z Deliver of Simple Parenteral Chemotherapy)	£432 (NHSE, based on COVID-19 monoclonal antibody infusion)

- Appendix: Aspects not captured in modelling

Abbreviations: AD, Alzheimer's disease; EQ-5D, EuroQol-5 domains; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre; NHSE, NHS England; TB-ALZ (2), TRAILBLAZER-ALZ (2)

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Cost-effectiveness results: revised base cases

Company updated base case ICER <£20,000/QALY, EAG's preferred ICER is substantially higher

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

Technology	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,091
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

Table: Revised EAG base case (deterministic, revised PAS price)

Technology	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£135,284
BSC	[redacted]	[redacted]	-	-	-

Changes to company base case: Population, starting proportions, transition to residential care, mortality, long-term waning, outpatient visit costs for APOE4 testing and monitoring, terminal care costs, updated PAS price

Changes to EAG base case: Population, long-term waning, infusion cost, 10% of patients treated until amyloid clearance, updated PAS price

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Abbreviations: APOE4, apolipoprotein E 4; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Incr., incremental; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year

Cost-effectiveness results: EAG base case

EAG base case ICER is substantially above £30,000/QALY

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

Changes applied to company updated base case	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Company updated base case	[redacted]	[redacted]	£12,091
+ Source of clinical efficacy as TB-ALZ 2 + TB-ALZ meta-analysis	[redacted]	[redacted]	£14,618
+ Waning from cycle 5 for 10 cycles (full effect for 1 year after stopping, then 5 years waning)	[redacted]	[redacted]	£30,836
+ Mortality hazard ratios taken from Crowell 2023	[redacted]	[redacted]	£42,522
+ Patient utility from GERAS study	[redacted]	[redacted]	£47,879
+ Caregiver disutility from GERAS study with 1.2 caregivers	[redacted]	[redacted]	£76,617
+ Infusion cost for donanemab: £432 (NHSE)	[redacted]	[redacted]	£89,144
+ Patients starting in health states: MCI 20.4%, Mild AD 79.6%	[redacted]	[redacted]	£125,961
+ Health care resource use does not include unpaid care costs	[redacted]	[redacted]	£135,284
EAG base case	[redacted]	[redacted]	£135,284

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; Incr., incremental; MCI, mild cognitive impairment; NHSE, NHS England; PAS, patient access scheme; QALY, quality-adjusted life year; TB-ALZ (2), TRAILBLAZER-ALZ (2)

Cost-effectiveness results: EAG scenarios

All EAG scenarios are substantially above £30,000/QALY

Table: EAG scenario analyses (deterministic, updated PAS price)

No.	Scenario (applied to revised EAG base case)	ICER (£/QALY)
EAG base case		£135,284
1	Source of clinical efficacy as TB-ALZ 2 only (UK eligible)	£124,496
2	Fixed 18-month duration of treatment only (0% treat to clear)	£136,852
3	Waning from cycle 11 for 18 cycles (full effect for 4 years after stopping, then 9 years waning)	£92,039
4	Waning from cycle 11 for 10 cycles (full effect for 4 years after stopping, then 5 years waning)	£97,376
5	Waning from cycle 7 for 10 cycles (full effect for 2 years after stopping, then 5 years waning)	£115,975
6	Mortality risk for AD from NACC analysis	£150,893
7	Mortality risk for AD from Ross et al.	£150,935
8	Mortality risk for AD from Lin et al.	£139,748

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme; QALY, quality-adjusted life year; TB-ALZ 2, TRAILBLAZER-ALZ 2

Cost-effectiveness results: EAG scenarios

All EAG scenarios are substantially above £30,000/QALY

Table: EAG scenario analyses (deterministic, updated PAS price)

No.	Scenario (applied to revised EAG base case)	ICER (£/QALY)
EAG base case		£135,284
9	Patient utility values taken from Landeiro et al.	£102,581
10	Carer utility values: EAG scenario 1 (Table 5 of EAG critique)	£105,586
11	Carer utility values: EAG scenario 2 (Table 5 of EAG critique)	£104,517
12	Carer utility values taken from Belger et al. vignettes with 1.8 caregivers	£79,920
13	1.4 caregivers	£134,218
14	1.6 caregivers	£133,169
15	Infusion cost for donanemab of £207.59	£120,439
16	At model entry: 70% MCI due to AD / 30% mild AD dementia	£102,807
17	Include unpaid carer costs	£125,961

- Appendix: Company scenarios

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme; QALY, quality-adjusted life year

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

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

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Equality considerations

Key themes are diagnosis, risk factors and treatment of AD and NHS capacity

Individual disadvantages

- People without a caregiver who can help them get timely diagnosis
- Those with lower educational attainment score lower on MMSE – impacts eligibility

Population inequality in diagnosis and accessing care

- Need to test for biomarkers will act as a barrier to treatment, 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: 50% to 90%
- People with more agency and resources find it easier to 'adhere' to the complex diagnosis and treatment pathway, which includes need for several eligibility and monitoring tests and having regular infusions

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 unlikely to be included in trial due to age cut-off of 60 years or older
- Some people with young-onset dementia excluded due to trial lower age-limit
- Some ethnic groups were under-represented in trial

NHS capacity and service delivery considerations

- NHS capacity likely to impact access
- "Opportunity cost created by [these] drugs would also increase health inequalities, as services under existing strain would be massively distracted by attempting to deliver this treatment. As services decline the effect is always seen more profoundly for those from more deprived socioeconomic circumstances"

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Abbreviations: AD, Alzheimer's disease; MMSE, mini metal sate examination

Company's updated managed access proposal

Company

Table: TRAILBLAZER studies providing longer term data

Study	Design (results expected)
TB-ALZ 2 EXT + Addendum 11	Clinical efficacy in delayed start patients ([redacted]) + Amyloid reaccumulation rate over up to 48 months ([redacted])
TB-ALZ 5	Clinical efficacy over 18 months including changes in amyloid deposition, quality of life, resource use ([redacted])
TB-REAL-Global	Long-term comparative effectiveness study (donanemab vs. usual care) over 5 years (3 year data available ~2029)

Real world evidence sources include:

On long-term effectiveness and safety:

- International Registry for Alzheimer's Disease and other Dementias (InRAD) https://www.inradnetwork.org/
- Platform for Early Alzheimer's in Real Life (PEARL) 5-years retrospective and 5-years prospective ([redacted])

Real world evidence sources continued:

On healthcare costs and resource use in UK:

- Alzheimer's Cost and HCRU Study (retrospective) (Q1 2025)
- Implementation of ATTs Cost & HCRU Study (retrospective, UK) (Q1 2027)
- UK Controlled Access Program, to register all patients prior to initiation of donanemab, promoting safe and effective use (N/A)

Other supplementary data collection programs:

- Post-Authorisation Safety Study (PASS, 200 UK patients)
- Understanding donanemab target patient (EU and UK, Q1 2027)
- Real world effectiveness of donanemab (EU and UK, Q2 2028)
- [redacted]

Abbreviations: AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormality; ATT, amyloid-targeting treatments; HCRU, healthcare resource utilisation; MCI, mild cognitive impairment; N/A, not available; Q, quarter; TB-ALZ (2 or 5), TRAILBLAZER-ALZ (2 or 5)

Summary of managed access team feasibility assessment

Is Managed Access appropriate – Overall rating	Comments and Rationale
Committee judgement required	• Ongoing trials could generate further evidence to resolve some uncertainties, but several would not be addressed at all, and some only partly addressed • No NHS-level data collection is proposed beyond baseline characteristics on enrolment, so the most feasible way to gather further data may be via the described trials rather than real-world data in clinical practice • The burden of implementation is significant with or without data collection • Several key questions remain

- Appendix: Criteria applied by NICE committee

Abbreviations: IMF, Innovative Medicines Fund; MAA, Managed Access Agreement; NHSE, NHS England; PET, positron emission tomography; RWE, real-world evidence

Managed access: Questions to committee

- Does the committee consider donanemab is plausibly cost-effective?
- Does the committee believe that managed access as proposed by the company will resolve its uncertainties?
- Are uncertainties not addressed by the proposal sufficiently addressed elsewhere in the appraisal?
- Are any additions needed to make the managed access proposal sufficiently powerful? E.g. would the proposal require long-term RWE data collection across the NHS to adequately resolve your uncertainties?
- Are any items in the proposal unnecessary? I.e. does the proposal need to be implemented as described or would the committee select only certain elements?
- Can/should uncertainty be resolved another way, e.g. by improving cost-effectiveness? This would reduce the suitability of managed access as a solution
- Can data from a single UK SDE be extrapolated to the whole NHS population, or would treatment in different centres be too varied?

Abbreviations: RWE, real-world evidence; SDE, Secure Data Environment

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

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

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Key issues

Issue	Question for committee	Slide
Modelling clinical effectiveness	Which analysis of trial results does the committee preferred to use to inform the model?	12-13
Hazard ratios for mortality by Alzheimer's disease severity	Is the company's approach to predicting mortality is suitable for decision making?	14-15
Long term treatment effect assumptions	Are the company's long-term treatment assumptions reasonable? What is the committee's preferred approach?	16-17
Patient utilities	Are proxy utility values acceptable for decision making? Which estimates are preferred (previously EAG)?	18
Carer utilities	Which estimates are preferred (previously EAG)? How many caregivers should be assumed?	19-20
Health state occupancy at start of model	Are the company's assumptions reasonable? Would most people eligible for donanemab start treatment when they have MCI?	21
Modelled costs: company, EAG and NHSE	Are the company's cost assumptions for diagnosis reasonable? Which infusion cost should be used in decision-making?	22

Abbreviations: EAG, evidence assessment group; MCI, mild cognitive impairment; NHSE, NHS England;

Thank you

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

Supplementary appendix

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Back to main deck: Committee conclusions at ACM1

Committee conclusions at ACM1 – recommendation and uncertainties identified

Committee recommendation

"The committee acknowledged the **high uncertainty** associated with the modelling, including in the long-term evidence for donanemab. It decided that **more evidence was needed** to generate robust cost-effectiveness estimates. It noted that the EAG's and company's base cases were associated with uncertainty, and the **most plausible** cost-effectiveness estimates were **above the range** normally considered a cost-effective use of NHS resources. So, it **did not recommend donanemab** for treating mild cognitive impairment or 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 identified substantial uncertainties

- treatment-effect estimates
- mortality risk associated with Alzheimer's disease
- how long the effects of donanemab last after stopping treatment
- health-related quality of life of people living with mild cognitive impairment and mild dementia caused by Alzheimer's disease and their carers
- infusion costs for donanemab

Abbreviations: ACM1, 1st committee meeting; APOE4, apolipoprotein E 4; EAG, evidence assessment group

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 disease	~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 – biomarker needed to confirm AD) → amyloid deposits form plaques and disrupt the function of brain cells
- NIA-AA guidelines used in the pivotal trial to stage cognitive impairment:

Mild cognitive impairment: Mild changes in memory and thinking are noticeable and measurable, but do not disrupt a person's day-to-day life	**Dementia:** Impairments in memory, thinking and behaviour decrease a person's ability to function independently in everyday life. Can be **mild, moderate or severe**

- Apolipoprotein E4 (APOE4) gene increases an individual's risk for developing Alzheimer's disease

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging and Alzheimer's Association

Back to main deck: Clinical effectiveness in indicated population

Donanemab (Kisunla, Eli Lilly & Co)

Note: First committee meeting held before final marketing authorisation was known, so committee considered full TB-ALZ 2 trial population

Marketing authorisation	• For treating: 'mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers'. October 2024
Mechanism of action	• In AD, clumps of amyloid beta protein form plaques in the brain. Donanemab works by binding to these clumps and reducing them
Needed before starting treatment	• Confirmation of beta amyloid (Aβ) consistent with Alzheimer's disease, by PET or CSF • Test for APOE4 status, with appropriate counselling and consent • Recent (within 1 year) brain MRI, then MRI before 2nd dose, dose increase, and 7th dose
Controlled access	• Initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme
Administration	• IV infusion over at least 30 minutes. After infusion, patients observed for at least 30 minutes • Recommended 700mg Q4W for first 3 doses, then 1,400mg Q4W per dose • Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible • If progression to moderate Alzheimer's disease before 18 months, treatment should be stopped
Price	• List price [redacted]/vial (350mg); 18 months treatment [redacted]. Patient access scheme applies

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; CSF, cerebrospinal fluid; IV, intravenous; MA, marketing authorisation; MRI, magnetic resonance imaging; PET, positron emission tomography; Q4W, every 4 weeks; TB-ALZ 2, TRAILBLAZER-ALZ 2

Back to main deck: Clinical effectiveness in indicated population

Key clinical trials

TRAILBLAZER-ALZ 2 is the phase 3 trial of donanemab used in company base case

Table: Features of the key donanemab trials

Trial	TRAILBLAZER-ALZ 2 (TB-AZL 2)	TRAILBLAZER-ALZ (TB-ALZ)
Design	Phase 3, randomised, double-blind	Phase 2, randomised, double-blind
Population	Adults with early symptomatic AD	Adults with early symptomatic AD
Comparison	Donanemab vs placebo	Donanemab vs placebo
Duration	18 months*	18 months*
Primary outcome	Change in iADRS at 18 months	Change in iADRS at 18 months
Key secondary outcomes	Change in CDR-SB, ADAS-Cog_{13}, ADCS-iADL, MMSE, amyloid PET	Change in CDR-SB, ADAS-Cog_{13}, ADCS-iADL, MMSE, amyloid PET
Sites include UK?	Yes	No (US and Canada)
Use in model	**Yes – updated company base case:** UK eligible population of TB-ALZ 2	Company scenario: UK eligible population of meta-analysis of TB-ALZ and TB-ALZ 2
Open-label extension data	Expected [redacted] for giving extra 18+ months follow-up	TB-ALZ EXT (Evans et al 2023): includes iADRS, CDR-SB & amyloid level ~18 months after stopping

Abbreviations: AD, Alzheimer's disease; ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale–Cognitive; ADCS-iADL, Alzheimer's disease cooperative study-activities of daily living; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, integrated Alzheimer's disease rating scale; MMSE, mini-metal stat exam; PET, positron emission tomography; TB-ALZ (2), TRAILBLAZER-ALZ (2)

Back to main deck: Summary of consultation responses

Consultation responses – patient and professional orgs (1)

Association of British Neurologists:

- Arguable whether costs of diagnostic testing (CSF and amyloid PET) should be included - already in NG97
- Unclear why severity modifier was not applicable
- Unclear why it is not appropriate to include informal care costs and impacts on quality of life for carers, suggest a non-reference case approach to reflect these costs accurately
- Uncertain of the basis for difference in infusion costs between company and NHSE
- Consider likelihood of people stopping donanemab before 18 months due to having evidence of amyloid clearance by PET to be much less than 10%. Suggests assuming none have these PET scans
- Encourage further discussions on managed access, including collection of real-world long-term data

Alzheimer's Research UK:

- Encourage consideration of longer-term data, including some expected soon – to inform this evaluation, and further discussions on managed access
- 3 clinicians estimated donanemab infusion costs to be £250 to < £500
- Uncertain how model addressed quality of life of carers, potential for non-reference case approach?
- Concern that donanemab not eligible for the severity modifier

Abbreviations: CSF, cerebrospinal fluid; NG97, NICE guideline 97; NHSE, NHS England; PET, positron emission tomography

Consultation responses – patient and professional orgs (2)

College of Mental Health Pharmacy:

- Recommendation is suitable and considers all relevant evidence. Members highlighted that <3 point change in iADRS over trial is less than considered meaningful in MCI (5 points) or mild AD (9 points)
- Need to develop specialist diagnostic clinics to identify early stage of AD
- System costs not clearly defined and need to be developed, including for delivery and monitoring of monoclonal antibody infusion, access / availability of PET scanning, acute medical services (side effects)
- Any recommendation should consider barriers to accessing treatment
- Impact of APOE4 allele testing, including through private genomic testing, and need for counselling
- Need longer term data on outcomes, impact of adverse events, wider cost of treatment to system

Alzheimer's Society:

- Encourage monitoring of longer-term data and real-world evidence
- Preventative care for Alzheimer's disease is not prioritised
- Inequalities due to significant service impacts and people excluded from TRAILBLAZER-ALZ 2 trial
- Summarised new evidence forecasting size of AD population and healthcare resource utilisation and care costs by dementia severity, and carer population size and scale of economic impact on carers

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; CSF, cerebrospinal fluid; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; PET, positron emission tomography; TB-ALZ 2, TRAILBLAZER-ALZ 2

Consultation responses – patient and professional orgs (3)

Royal College of Psychiatrists:

- Asks whether managed access is a feasible option including in helping to:
  - address uncertainties in evidence about real world efficacy and safety including subgroup analyses
  - establish diagnostic and treatment infrastructure that currently needs developing
  - understand cost impact of future developments (blood-based biomarkers, subcutaneous treatment)

Faculty of Public Health:

- Need to consider trial exclusion criteria and screen failure rate – impacts generalisability to UK clinical population who are on average 10 years older (discussed in slides)
- Guidance conclusion about trial generalisability is based on clinical expert opinion not empirical evidence
- Guidance statement that all people with MCI will progress to dementia – need for empirical evidence here
- Reiterated that empirical evidence shows donanemab treatment effect is not clinically meaningful
- Censoring for ARIA and infusion-related reactions corrects for unblinding, but will exacerbate attrition bias (only people who are doing well on treatment are included at later timepoints in analysis)
- Any long-term impact of short-term adverse effects (haemorrhages and brain shrinkage) unclear
- Unclear how costs of treatment eligibility testing is captured, including who has outpatient consultant visit

Abbreviations: ARIA, amyloid related imaging abnormalities; MCI, mild cognitive impairment

Back to main deck: Summary of consultation responses

Consultation responses – patient and professional orgs (4) and comparator company

UK Clinical Pharmacy Association – Neurosciences Committee:

- Some concerns around service capacity, including outpatient visits, lumbar puncture, genetic testing
    - Delay in diagnosis can limit access due to progression of the disease (to becoming ineligible)
    - Different service capacities in different areas, which impact access to treatment
- People with Down syndrome, young onset dementia and some ethnic groups not adequately represented in the trials – poses a risk of potential adverse impact that has not been established yet
- Need for investment and remodelling of the service for people who might be eligible for donanemab, but also for those with more advance disease, so this should be considered in evaluating population benefit
- Since PET is not mandatory to start donanemab and the limited availability of PET scans in the country, it is unlikely that patients will stop treatment before 18 months due to clearance
- Agree that mortality is higher in severe AD and this should be taken into account in predicting mortality

Comparator company for donepezil – Eisai (also lecanemab)

- Notes inconsistent cost assumptions compared with lecanemab appraisals for whether genetic counselling included separately and number of on-treatment outpatient monitoring visits (discussed in slides)

Abbreviations: AD, Alzheimer's disease; PET, positron emission tomography

Consultation responses – summary of web comments

"Negative recommendation is suitable" – 3 responses

- High degree of uncertainty in both clinical evidence and economic modelling, including in long term effects
- Need for meta-analysis and associated sensitivity analysis to allow a full interpretation of the evidence base including to evaluate risk of bias
- Considerable concerns with safety and efficacy of donanemab. Any future positive NICE recommendations need to include clearly defined stopping criteria based on efficacy as well as safety
- Currently there is a lack of capacity and infrastructure in the NHS, including in specialised services (MRI, PET-CT, lumbar puncture, genetic testing and counselling) to ensure safe and equitable use of donanemab
- Further assessment of psychological impact of APOE4 testing needed with need for genetic counselling
- Benefits too small to justify high costs which would divert resources from other treatments
- Recognise huge system impact on NHS if recommended, would need funding variation to ensure readiness
- Guidance incorrectly states that MCI always leads to AD

"Negative recommendation is not suitable" – 2 responses

- Committee did not have enough input from carers and people with Alzheimer's disease in making decision
- Costs/benefits in quality of life for person with Alzheimer's disease and carer, care home and end of life care savings not clear
- Wider picture has largely been ignored – timely diagnosis leads to reduced use of NHS resource
- Allow those with an early AD/MCI diagnosis to participate in an NHS backed study

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography

Back to main deck: NHS England consultation response

Consultation responses – NHS England, infusion costs

Donanemab infusion cost: 1st committee meeting

Previous : £565

- Previous NHSE approach estimated £565 per infusion
  - No NHS price for infusion, so estimated from current coding guidance to reflect most likely cost charged as X292: Continuous IV infusion of therapeutic substance NEC
  - Person's diagnosis and day attendance are primary drivers of cost, rather than the procedure itself
  - Appropriate OPCS code was X292: Continuous IV infusion of therapeutic substance NEC

Donanemab infusion cost: 2nd committee meeting

Updated : £432

- Updated NHSE approach estimates £432 per infusion
- Not possible to accurately estimate cost because it is not used in clinical practice and activity in research settings is not comparable to NHS clinical practice
- Pricing approach now assumes same infusion cost as with COVID-19 monoclonal antibody infusion:
  - Pricing supported by bottom-up costing work based on actual clinical practice
  - Reflects specific resource implications of a monoclonal antibody (like donanemab) not other drugs
  - Possible for this code to be actually used when administering donanemab in NHS practice
- Inappropriate to use chemotherapy infusion cost as a proxy (company approach)
  - Donanemab requires more complex preparation, higher risk of adverse infusion reaction, used in older people who may have more complex needs

Abbreviations: AD, Alzheimer's disease; IV, intravenous; OPCS, operating procedure codes supplement

Clinical effectiveness results (UK eligible population)

Results from meta-analysis similar to results from TRAILBLAZER-ALZ 2 only

Company

Table: Primary and key secondary outcome results at 18 months – UK eligible population

Outcome	TB-ALZ 2 only				Meta-analysis of TB-ALZ 2 and TB-ALZ			
	iADRS		CDR-SB		iADRS		CDR-SB	
Treatment arm	Donanemab	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab	Placebo
N at Baseline, Wk 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural cubic spline with 2 degrees of freedom (NCS2) analysis:								
LS mean change, Baseline to Wk 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI) [p-value]	[redacted] [<0.001]		[redacted] [<0.001]		[redacted] [<0.001]		[redacted] [<0.001]	
Progression slowed	[redacted]		[redacted]		[redacted]		[redacted]	
Mixed models for repeated measures (MMRM) analysis:								
LS mean change, Baseline to Wk 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI) [p-value]	[redacted] [<0.0001]		[redacted] [<0.0001]		[redacted] [<0.0001]		[redacted] [<0.0001]	
Progression slowed	[redacted]		[redacted]		[redacted]		[redacted]	

- iADRS worsening = decrease in score; CDR-SB worsening = increase in score

Abbreviations: See slide notes

Key issue: Potential impact of risk of bias in trials

Company provided sensitivity analysis with censoring for first ARIA and IRR

Committee at ACM1

- Having ARIA events or infusion-related reactions could affect how patients and their carers scored clinical outcomes, which leads to uncertainty in the treatment-effect estimates… company should explore this further through sensitivity analysis

Company

- There are no significant differences between censored and non-censored results, so risk of bias within the results is low

Table: HRs for disease progression with censoring for first ARIA and infusion-related reactions (UK eligible population)

Source	Measure	HR (95% CI)
TB-ALZ 2 censored	CDR-SB	[redacted]
	iADRS	[redacted]
Meta-analysis censored	CDR-SB	[redacted]
	iADRS	[redacted]

Faculty of Public Health comments

- Censoring corrects for unblinding, but will exacerbate attrition bias (only people who are doing well on treatment are included at later timepoints in analysis)

EAG comments

- Censoring [redacted]
- Overall, reassured that if occurrence of ARIA events did cause participants or their carers to predict they were having donanemab this did not have a substantial impact on trial outcomes

Abbreviations: ARIA, amyloid-related imaging abnormalities; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CI, confidence interval; HR, hazard ratio; iADRS, Integrated Alzheimer's Disease Rating Scale; TB-ALZ 2, TRAILBLAZER-ALZ 2

Key issue: Impact of APOE4 allele status

Company conducted analyses to explore impact of APOE4 status

Committee at ACM1

- The committee concluded it would like to see a sensitivity analysis based on TRAILBLAZER-ALZ 2 APOE4 allele subgroup results [Note: this request was based on anticipated marketing authorisation]

Company approach based on final marketing authorisation

- Mean change from baseline at Week 76 between treatment arms showed no statistically significant subgroup interaction
- HRs for disease progression similar for both subgroups
- No evidence APOE4 status 'non-carrier' vs 'heterozygous' is treatment effect modifier

Table: HRs for disease progression (UK eligible population)

Source	Subgroup	CDR-SB HR (95% CI)	iADRS HR (95% CI)
TB-ALZ 2	Non-carriers	[redacted]	[redacted]
	Heterozygotes	[redacted]	[redacted]
Meta-analysis	Non-carriers	[redacted]	[redacted]
	Heterozygotes	[redacted]	[redacted]

EAG comments

- APOE4 homozygotes excluded in confirmed marketing authorisation. No further comments on this issue

Abbreviations: APOE4, apolipoprotein E 4; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CI, confidence interval; HR, hazard ratio; iADRS, Integrated Alzheimer's Disease Rating Scale; TB-ALZ 2, TRAILBLAZER-ALZ 2

Back to main deck: Hazard ratios for mortality

Large ICER impact

Hazard ratios for mortality by AD severity

Company updated base case to incorporate variable mortality risk by AD severity

Table: Mortality risk compared with general population

Health state	**Company updated base case** (NACC data)	Ross et al.	Lin et al.	**EAG base case** (Crowell et al. NACC data) – age 80 years
MCI	1	1.61	1.82	1
Mild AD	1.79	2.23	2.92	2.4
Moderate AD	1.75	3.10	3.85	3.1
Severe AD	3.41	4.98	9.52	6.6

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

Back to main deck: Patient utilities

Large ICER impact

Patient utility values

Company and EAG approaches presented at 1st committee meeting

Table: Patient utility values (proxy reported)

Health state	Company model (Landeiro et al)	EAG base case (GERAS, overall)	EAG scenario (GERAS, UK)
MCI	0.76	0.77	0.76
Mild AD	0.74	0.71	0.68
Moderate AD	0.59	0.64	0.65
Severe AD	0.36	0.51	0.48

Company – late consultation comments

- Submitted re-analysis of GERAS values after consultation period closed, which has not been critiqued by EAG
- Provided adjustment to GERAS values that aligns MMSE categories with those used for modelled health states
- Adjusted moderate and severe AD values are between company and EAG base case values (not applied in model or scenario analysis). MCI not adjusted

Table: Patient utility values (proxy reported) – GERAS

Health state	EAG base case (GERAS, overall)	Company's re-analysis of GERAS values*
MCI	0.77	No change
Mild AD	0.71 [MMSE 21 to 26]	0.70 [MMSE 20 to 26]
Moderate AD	0.64 [MMSE 15 to 20]	0.60 [MMSE 10 to 19]
Severe AD	0.51 [MMSE score <15]	0.45 [MMSE score <10]

*Mean values with N = 677 mild, 633 moderate and 185 severe AD

NICE

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; MMSE, mini mental state exam

Back to main deck: Caregiver utilities

Large ICER impact (values)

Caregiver utility values

Company and EAG approaches presented at 1st committee meeting

Table: Caregiver utilities in Company base case

Health state	Community	Residential
Child caregiver (as proxy for not living with patient)		
MCI	0.84	0.84
Mild AD	0.78	0.78
Moderate AD	0.62	0.71
Severe AD	0.46	0.64
Spouse caregiver (as proxy for living with patient)		
MCI	0.82	0.82
Mild AD	0.72	0.72
Moderate AD	0.54	0.71
Severe AD	0.38	0.64

Table: Caregiver utilities in EAG base case

Health state	GERAS adjusted
	All
MCI	0.81*
Mild AD	0.80*
Moderate AD	0.79
Severe AD	0.76

*General population utility used since GERAS value > general population

Table: Caregiver utilities in EAG scenarios based on company's vignettes

Health state	Spouse – Community	Child – Community, All – Residential
MCI	0.82	0.84
Mild AD	0.79	0.74
Moderate AD	0.65	0.71
Severe AD	0.49	0.64

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment

Back to main deck: EAG scenarios

Cost-effectiveness results: company scenarios

All company scenarios are below £20,000/QALY except removing unpaid care

Table: Company revised scenario analyses (deterministic, updated PAS price)

No.	Scenario (applied to revised company base case)	ICER (£/QALY)
Company updated base case		£12,091
1	Clinical data from meta-analysis of TB-ALZ 2 and TB-ALZ	£14,618
2	At model entry: 49.3% MCI due to AD / 50.7% mild AD dementia	£16,445
3	At model entry: 38% MCI due to AD / 62% mild AD dementia*	£19,119
4	Fixed 18-month duration of treatment only (0% treat to clear)	£12,490
5	15% of patients treated until amyloid clearance	£11,888
6	Treatment waning over 11 years, after 5.5 years full effect	£11,556
7	Treatment waning over 7 years, after 5.5 years full effect	£12,871
8	Treatment waning over 5 years, after 5.5 years full effect	£14,057
9	Treatment waning over 3 years, after 5.5 years full effect	£15,955

*Lecanemab appraisal

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme; QALY, quality-adjusted life year; TB-ALZ (2), TRAILBLAZER-ALZ (2)

Back to main deck: EAG scenarios

Cost-effectiveness results: company scenarios

All company scenarios are below £20,000/QALY except removing unpaid care

Table: Company revised scenario analyses (deterministic, update PAS price)

No.	Scenario (applied to revised company base case)	ICER (£/QALY)
Company updated base case		£12,091
10	EAG alternative approach to using company's vignette study for caregiver utility	£13,476
11	1.6 carers per patient	£12,687
12	1.4 carers per patient	£13,344
13	1.2 carers per patient	£14,073
14	Excluding unpaid care costs	£21,357
15	IV infusion cost: Neurology Consultant-Led (first attendance) Outpatient Attendance (£222.91)	£12,368
16	IV infusion cost: SB13Z Delivery of Complex Parenteral Chemotherapy (£256.95)	£12,984

Abbreviations: AD, Alzheimer's disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; IV, intravenous; PAS, patient access scheme; QALY, quality-adjusted life year

Aspects not captured in modelling

Uncaptured impact on patients, carers, and NHS services

Company: having access to a new technology

- For patients, this works to reduce the fear of AD
- Will lead to overall improvements in the care provided for all patients with dementia

Faculty of Public Health: potential false hope

- False hope for people tested but not suitable for treatment
- Emotional burden for people who test APOE4 homozygous

UCL Dementia Research Centre: burdens of treatment

- Very significant burdens for patients and caregivers from need for frequent IV infusions and MRI scans

Company: impact on carers

- Patients typically become dependent on caregiver for their everyday functioning, which makes burden on caregiver an essential aspect of the disease
- Disconnect between NICE's reference case perspective, which includes both patient and caregiver QALYs, and the calculation of the severity modifier which excludes caregiver quality of life

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

Alzheimer's society & Alzheimer's Research UK: impact on carers

- Submitted evidence for impact of dementia on the finances and productivity of carers scans

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; QALY, quality-adjusted life year

Back to main deck: Summary of managed access team feasibility assessment

Criteria applied by NICE committee

Committee can make a recommendation with managed access when:

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

When making a recommendation with managed access, committee should:

- Identify **uncertainties** to be addressed, from which **data sources**, over what **time frame**