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

For committee – contains [redacted] information

Third appraisal committee meeting

Technology appraisal committee D [14 May 2025]

Chair: Dr Megan John

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

- ✓ **Recap from ACM2**
- ✓ Consultation responses (excluding company)
- ❑ Company response and EAG critique
- ❑ Cost effectiveness results
- ❑ Other considerations
- ❑ Summary

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Donanemab (Kisunla, Eli Lilly & Co)

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	• Accumulation of amyloid-beta (Aβ) plaques + tau tangles characterise Alzheimer's disease • Donanemab is a humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against Aβ, marking it for immune system to clear • May reduce levels of tau, another biomarker of AD, in the brain
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 • Updated PAS for ACM3

Abbreviations: ACM3, 3rd committee meeting; APOE4, apolipoprotein E 4; CSF, cerebrospinal fluid; IV, intravenous; MRI, magnetic resonance imaging; PET, positron emission tomography; Q4W, every 4 weeks; PAS, patients access scheme; TB-ALZ 2, TRAILBLAZER-ALZ 2

Committee conclusions at 2nd committee meeting (AMC2)

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

Summary of committee conclusion:

- Significant unmet need for treatment options and high uncertainty associated with the modelling, including in the long-term evidence
- Most plausible cost-effectiveness estimates considerably above the range normally considered a cost-effective use of NHS resources
- Committee decided that the modest benefit to patients demonstrated in the trial, balanced with the decision-risk associated with the substantial resources the NHS would need to commit to implement access to donanemab would be too great, even with a managed access agreement
- Donanemab was not cost effective so managed access recommendation could not be made. Committee concerned additional data collection would not resolve the uncertainties
- Did not recommend donanemab either for routine NHS use or with managed access

Consultation responses received from:

Company (Eli Lilly), Alzheimer's Research UK, Alzheimer's Society, Association of British Neurologists, UK Clinical Pharmacy Association – Neurosciences Committee, UCL Dementia Research Centre, Web comments (n=2)

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Abbreviations: ACM2, 2nd committee meeting; UCL, University College London

Committee identified uncertainties in modelling at ACM2

Committee identified substantial uncertainties:

Uncertainty at ACM2	New evidence presented by company?
Treatment effect estimates	No (but see LTE below)
What proportion of people starting donanemab would have MCI or mild dementia caused by AD	Yes: from controlled access program
Risk of death associated with AD	No
How long the effects of donanemab last	Yes: from TB-ALZ 2 LTE versus external control arm
Health-related quality of life of people with MCI or mild dementia caused by AD, and their carers	Yes: on caregiver utilities
Infusion costs for donanemab	Yes

Abbreviations: ACM2, second committee meeting; AD, Alzheimer's disease; LTE, long term extension; MCI, mild cognitive impairment; TB-ALZ 2, TRAILBLAZER-ALZ 2

Key issues to discuss at ACM3

Key issue	Company approach for discussion	ICER impact*
Long-term effects	No change to base case. Presents further evidence	Large
Caregiver utilities	No change to base case. Presents further evidence	Large
Model starting proportions	Company's modelling assumption updated	Moderate
Infusion cost	No change to base case. Presents further arguments	Large

*ICER impact based on changing the variable in EAG base case: high impact is >£10,000/QALY difference in ICER, moderate impact is >£5,000/QALY difference in ICER

Abbreviations: ACM2, 2nd committee meeting; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TB-ALZ 2, TRAILBLAZER-ALZ 2

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Organisations and more detailed responses in Appendix (slide #37-41)

Summary of consultation responses

Diagnosis and management

- **Use of biomarkers:** CSF biomarkers not routine in practice. Impact of blood biomarkers unclear
- **APOE4 testing:** More clarity on support for patients and families
- **Services:** burden on infusion unit and outpatients. Need for training

Trial results

- **Excluded:** people with Down's syndrome or young-onset AD
- Need for ongoing review of **long-term data**

Severity modifier:

- Concern severity modifier not applied (RECAP: QALY shortfall calculations #55)

Cost-effectiveness modelling

- **Increasing diagnosis of MCI:** possible shift towards this as awareness of potential DMTs grows
- **Caregiver QoL:** True impact not being incorporated, particularly caring for people in later stage of Alzheimer's disease
- **Infusion cost** uncertainty
- Appropriateness of excluding **informal care costs**

Wider considerations

- **Timely diagnosis:** could lead to less use of NHS resources
- **Treatment effect:** Relatively moderate gains compared to risk and burden. Is investment better directed to improving pathways and care for all, rather than only those eligible for donanemab?
- **Managed access** would allow for fast-tracked diagnosis, real world and longer term data collection on efficacy and safety, infrastructure development and greater understating of system-level costs in implementation

- Some further responses under Key issues: TB ALZ-2 long term effects, Carer utilities, Starting proportions

Abbreviations: APOE4, apolipoprotein E 4; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; MCI, mild cognitive impairment; NHSE, NHS England; PET, positron emission tomography; QALY, quality-adjusted life year; QoL, quality of life

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TB-ALZ 2 long-term extension data and external arm comparison

Treatment effect of donanemab goes beyond the 18-month treatment duration

Company

- TB-ALZ 2 long-term extension ([redacted]) provides 3-year follow up for donanemab in UK eligible population
- Supports that treatment effect of donanemab goes beyond 18-month treatment duration, with absolute difference between arms increasing between 18 months and 36 months
- Comparison made with external control arm (Appendix slide #43: [redacted]) up to 36 months. Assumes disease progression of TB-ALZ 2 placebo arm would be same as for external control arm

Figure: MMRM analysis of adjusted mean change in CDR-SB score

Differences in CDR-SB (95% CI):

- [redacted] between **donanemab** and external control arm at 18 months,
- [redacted] between **donanemab** and external control arm at 36 months
- [redacted] between external control arm and **placebo** at 18 months

- Sensitivity analysis in patients with amyloid clearance at 6 months provides 2.5 years off-treatment follow up

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Abbreviations: [redacted] CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; MMRM: mixed models for repeated measures; N, number; TB-ALZ 2, TRAILBLAZER-ALZ 2

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Large ICER impact

Key issue: Long-term treatment effect assumptions

Company and EAG disagree on assumptions; EAG partly updates approach

Committee at ACM2

- Modelling is highly uncertain
- Preferred EAG's assumptions: 1-year full effect after stopping and 5 years waning (but this may be optimistic)

Association of British Neurologists:

- Further evidence needed
- Lag between amyloid re-accumulation and cognitive decline biologically plausible. Experts believe cognitive decline relates to downstream neurodegenerative effects of amyloid
- Treatment effects could continue after treatment is stopped

Company – approach unchanged

Appendix: RECAP of Long-term treatment effect assumptions

- Maintains: full effect for 5.5 years, gradual waning for 9 years (total effect 14.5 years)
- New data addresses uncertainty and validates company's approach
- UK eligible population in TB-ALZ 2 LTE indicates mean amyloid re-accumulation rate of ~[redacted], so 2.8 CL/year to inform assumptions conservative
- **Full effect:** considers EAG's approach based on length of TB-ALZ 2 trial arbitrary and not related to underlying pathology. Overly conservative – patient may still be 'amyloid negative' in comparable trials
- **Waning:** disagrees with way EAG applied 26–50 CL amyloid threshold (from van der Kell et al. 2021) as threshold for loss of treatment effect. Company considers 50 CL is more appropriate threshold for loss of treatment effect – 50 CL is threshold for propagation of downstream tau, primary mediator of amyloid-induced neurodegeneration, correlates with clinical and functional decline

Abbreviations: ACM2, 2nd committee meeting; CL, centiloids; EAG, evidence assessment group; LTE, long term extension; TB-ALZ 2, TRAILBLAZER-ALZ 2

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Large ICER impact

Key issue: Long-term treatment effect assumptions

EAG – assumption partly updated

Appendix: RECAP of Long-term treatment effect assumptions

- **Full effect:** increases duration to 4 years, which includes 2.5 years after stopping based on longest duration of effect observed after stopping treatment, in early amyloid clearance subgroup of TB-ALZ 2 LTE
- **Waning:** maintains assumption of gradual waning for 5 years (total effect 9 years)
- Scenario applying company's preferred long-term treatment effect assumptions to EAG's updated base case reduces EAG ICER from £67,891 to £57,811/QALY

EAG considered TB-ALZ 2 long-term extension data provides additional useful data but cautions that:

- Appears to include participants receiving donanemab beyond 18 months (those that did not meet treatment completion criteria) → treatment difference between 18 and 36 months could be lower in clinical practice
- Some concerns with company's external control arm used for comparison with donanemab (Appendix)
- Sensitivity analysis for 6-month clearers provides evidence for 2.5 years after stopping donanemab, but these participants might not be representative if: [redacted]

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

Large ICER impact

Key issue: Caregiver utilities

Company provides further justification of approach (unchanged)

Committee at ACM2

Next slide: RECAP of Caregiver utility values

- Preferred EAG's approach: utility values from GERAS (large UK study) appeared reasonable
- 1.8 caregivers appropriate (In line with GERAS)
- Utility values for caregivers of people with Alzheimer's disease are highly uncertain

Company – approach unchanged

- Derives values from 2 vignette studies split by spouse or child caregivers, community or residential setting
- Important impact on caregivers is adequately reflected in model. Company presents:
  - Psychometric properties of EQ-5D (appendix): Lack sensitivity. Also, GERAS results lack face validity
  - **Market research conducted among 26 caregivers** of people with AD in the UK. Suggested modelling of caregiver QoL does not adequately reflect difference in burden seen between carers of people with 'MCI or mild dementia' compared with carers of people with 'moderate or severe dementia'
  - **Findings from company's Alzheimer's Europe Caregiver Focus Group**, who were asked how well company's vignettes and the EQ-5D instrument reflected their own experience of being a caregiver. Concluded that vignettes provided better reflection of caregivers' perspective than EQ-5D

Abbreviations: ACM2, 2nd committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; QoL, quality of life; MCI, mild cognitive impairment

RECAP from ACM1 and ACM2

Caregiver utility values

Company and EAG approaches presented at 1st committee meeting

Table: Caregiver utilities in Company base case

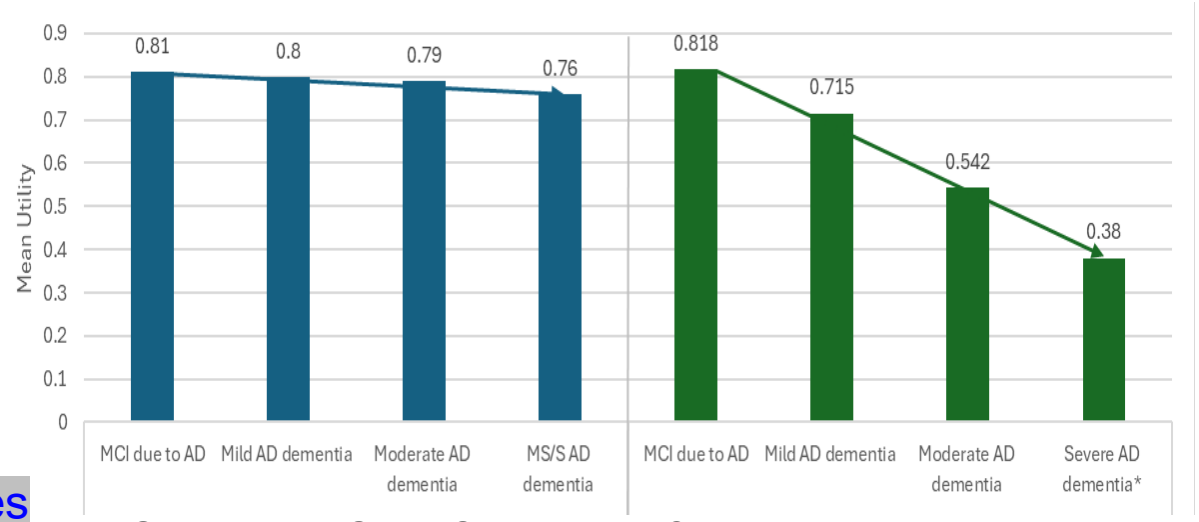
Health state	Community	Residential
Child caregiver (as proxy for not living with patient)		
MCI	0.84	0.84
Mild AD	0.78	0.78
Moderate AD	0.62	0.71
Severe AD	0.46	0.64
Spouse caregiver (as proxy for living with patient)		
MCI	0.82	0.82
Mild AD	0.72	0.72
Moderate AD	0.54	0.71
Severe AD	0.38	0.64

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 value used since GERAS value > general population
†Decrement applied to general population values

Figure: Comparison of EAG and company utility values



- Appendix: EAG scenario based on company vignettes

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Abbreviations: ACM1/2, 1st / 2nd committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; MCI, mild cognitive impairment

Large ICER impact

Key issue: Caregiver utilities

EAG preferred values unchanged, but updates to aligns on caregiver number

EAG – values unchanged, caregiver number updated to 1.8

- Acknowledge significant burden on caregivers of patients with moderate and severe AD
- As previously stated by EAG, most aspects caregivers report to affect daily quality of life not directly related to health, therefore not relevant for HRQoL (exception is mental health, which is captured by EQ-5D)
- Previously reported limitations of company's vignette studies (Appendix: RECAP of Key issue at ACM2) and consider GERAS study is best available study for caregiver utilities for patients with AD
- Updated base case to 1.8 caregivers (aligns committee preference at ACM2)
- Model results most sensitive to using caregiver utilities from company vignettes. Scenario applying company's utility values to EAG's updated base case reduces EAG ICER from £67,891 to £43,621/QALY

Alzheimer's Research UK, Association of British Neurologists & Dementia Research Centre, UCL:

- True impact on carer QoL not being incorporated – questions appropriateness of using EQ-5D to measure it. Mobility, self-care and usual activities domains – little bearing on what carers describe as impact of caring
- Queries face validity of EAG's carer utility values with lack of change from MCI to moderate AD dementia. People with MCI have normal activities of daily living, while those with dementia need assistance → burden increase

Are the company's caregiver utility values reasonable? What is the committee's preferred approach?

Abbreviations: ACM2, 2nd committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; QALY, quality-adjusted life year; QoL, quality of life

Moderate ICER impact

Key issue: Health state occupancy at start of model

Company updates model starting health state proportion (= lecanemab DG2)

Committee at ACM2

- Preferred: 20.4% in MCI due to AD and 79.6% in mild AD patients (from TRAILBLAZER-ALZ 2 trial)

Company – updated to 38% in MCI due to AD and 62% in mild AD dementia

- Proportions considered most plausible in UK clinical practice by committee in lecanemab appraisal (DG2)
- Clinicians more likely to start treatment early and more likely in MCI (due to stopping rule at moderate AD and 18-month maximum treatment duration). Approach is conservative
- As of 12 May 2025, controlled access programme (condition of donanemab MHRA license) indicates [redacted] of UK patients initiated on donanemab have MCI due to AD and [redacted] have mild dementia due to AD – early indication that biomarker confirmation and availability of an effective treatment is likely to lead to earlier identification of patients and a higher proportion in MCI

EAG: – unchanged from 20.4% in MCI due to AD and 79.6% in mild AD dementia

- TB-ALZ 2 starting proportions* ~aligned source of treatment effect, which is different for MCI and mild AD
- Applying company's proportions to EAG base case reduces EAG ICER from £67,891 to £59,059/QALY

Association of British Neurologists & Dementia Research Centre, UCL: expect a shift to earlier presentation as awareness of potential DMTs grows, although opinions differ on whether this is seen already

*Overall population; proportions were 21% MCI and 79% mild AD in TB-ALZ 2 UK-eligible population, but were not provided for combined analysis with TB-ALZ

Are the company's updated assumptions reasonable?

Abbreviations: ACM2, 2nd committee meeting; AD, Alzheimer's disease; DG", draft guidance 2; DMT, disease modifying therapy; 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

Appendix: RECAP of ACM2 infusion costs

Large ICER impact

Key issue: Infusion costs – company and NHSE

Difference in costs estimated by the company and NHS England

Committee at ACM2:

- Cost should reflect the health system resources required for giving an infusion of donanemab
- Most appropriate cost is likely closer to NHS England estimate than company's but uncertainty
- Concluded it would use both company and NHSE estimates when considering most plausible ICER range

Company: **£208**

- As in ACM1 and 2, uses £207.59 (SB12Z Deliver of Simple Parenteral Chemotherapy). Provided scenarios
- Acknowledges uncertainty. Considers lack of transparency in how NHSE estimate was derived
- **Population:** COVID mAbs infusion cost for severely immunocompromised and medically complex patients while donanemab is a routine outpatient infusion for a chronic condition in medically stable patients
- **Preparation:** simple parental chemotherapy cost overestimates donanemab infusion cost compared with trastuzumab: hospital pharmacy (laminar flow hood), weight-based dosing, premedication, extensive monitoring
- **Monitoring for IRRs:** trastuzumab has substantially higher rate (40%) than donanemab (8.5%) and a higher risk of severe reactions associated with fatal outcomes

NHSE: **£432**

- See next slide for explanation

EAG **£432 = NHSE**

- Applying company cost to EAG base case reduces EAG ICER from £67,891 to £56,984/QALY

Abbreviations: EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; IRR, infusion-related reaction; MCI, mild cognitive impairment; mAbs, monoclonal antibodies; NHSE, NHS England

Large ICER impact

Key issue: Infusion costs – company and NHSE

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

NHS England: **£432**

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

Which infusion cost estimate does the committee prefer to use in the modelling?

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

Summary of company and EAG base case differences

Differences between company and EAG base cases at ACM3

Assumption	Company updated base case	EAG base case
Long-term treatment effect and waning	Full effect for 5.5 years Gradual waning for 9 years	Full effect for 4 years Gradual waning for 5 years
Caregiver utility (number)	2 vignette studies (1.8 caregivers)	GERAS study (1.8 caregivers)
Model starting proportion	38% MCI due to AD 62% mild AD	20.4% in MCI due to AD 79.6% in mild AD (from TB-ALZ 2)
Infusion cost	£207.59 (SB12Z Deliver of Simple Parenteral Chemotherapy)	£432 (NHSE, based on COVID-19 monoclonal antibody infusion)

- Note: company and EAG base cases are aligned on patient utility values at ACM3, both using values from company's reanalysis of GERAS study values with adjusted MMSE categories (see Appendix slide #46), which was the committee preference at ACM2

- **Second draft guidance consultation: no further equality issues** (Appendix slide #56 for RECAP) **or aspects not captured in modelling** (Appendix slide #57 for RECAP) **were raised**

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Abbreviations: ACM1/2/3, 1st/2nd/3rd committee meeting; AD, Alzheimer's disease; EQ-5D, EuroQol-5 domains; MCI, mild cognitive impairment; NHSE, NHS England

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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 than £20,000 to £30,000/QALY range

Table: Revised company base case for ACM3 (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]	£27,366
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

Table: Revised EAG base case for ACM3 (deterministic, revised PAS price)

Technology	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£67,891
BSC	[redacted]	[redacted]	-	-	-

Changes to company base case: source for modelling clinical effectiveness, mortality, patient utility values, model starting proportions, unpaid care costs excluded, updated PAS price

Changes to EAG base case: duration of full treatment effect, patient utility values, caregiver number, updated PAS price

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Abbreviations: ACM3, 3rd committee meeting; 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 higher than £20,000 to £30,000/QALY range

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]	£27,366
+ Waning from cycle 8 for 10 cycles (full effect for 2.5 year after stopping, then 5 years waning)	[redacted]	[redacted]	£31,948
+ Caregiver disutility from GERAS study with 1.8 caregivers	[redacted]	[redacted]	£48,898
+ Patients starting in health states: MCI 20.4%, Mild AD 79.6%	[redacted]	[redacted]	£56,984
+ Infusion cost for donanemab: £432 (NHSE)	[redacted]	[redacted]	£67,891
EAG base case	[redacted]	[redacted]	£67,891

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

Cost-effectiveness results: EAG scenarios

All EAG scenarios are substantially higher than £20,000 to £30,000/QALY range

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

No.	Scenario (applied to revised EAG base case)	ICER (£/QALY)
EAG base case		£67,891
1	Waning from cycle 11 for 18 cycles (full effect for 4 years after stopping, then 9 years waning)	£57,811
2	Carer utility values taken from company's vignettes	£43,621
3	Proportions at model entry: 38% MCI due to AD / 62% mild AD dementia	£59,059
4	Infusion cost for donanemab of £208	£56,984
5	DG2 committee preferred assumptions with infusion cost of £208[a]	£69,604
6	DG2 committee preferred assumptions with infusion cost of £432[a]	£83,011

[a]DG2 committee preferred EAG base case with waning after 5 cycles (2.5 years) for 10 cycles (5 years)

- Appendix: Company scenarios

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Abbreviations: AD, Alzheimer's disease; DG2, draft guidance 2; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme; QALY, quality-adjusted life year

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Company's updated managed access proposal

Company

Two key uncertainties would be fully resolved by managed access data collection:

- From UK Controlled Access Programme: proportion of patients initiating treatment within MCI due to AD or mild AD stages of model
- UK real-world evidence will provide information on IV infusion costs to resolve uncertainty

Table: TRAILBLAZER studies providing longer term data

Study	Design (results expected)
TB-ALZ 2 EXT (Addendum 11)	Annualised amyloid reaccumulation rate, up to 48 months (data availability [redacted])
TB-ALZ 5	Clinical efficacy over 18 months including changes in amyloid deposition, safety, quality of life, resource use ([redacted])
TB-REAL-Global	Comparative effectiveness 5-year study (vs. usual care) (3 year data ~2029)

Real world evidence sources:

Long-term effectiveness and safety:

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

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

Other supplementary data collection:

- Post-authorisation safety study (N=200 in UK)
- 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; ATT, amyloid-targeting treatments; HCRU, healthcare resource utilisation; IV, intravenous; MCI, mild cognitive impairment; N/A, not available; Q, quarter; TB-ALZ (2 or 5), TRAILBLAZER-ALZ (2 or 5); TBC, to be confirmed

Summary of managed access team feasibility assessment

Is Managed Access appropriate – Overall rating	Comments and Rationale*
Committee judgement required	Ongoing trials and observational studies could provide useful evidence to resolve remaining uncertainties at ACM3: • Longer-term efficacy: comparison will be between trial and observational data; Company's proposal describes strategy for mitigating this bias • Health state occupancy at the start of the model: Data from baseline NHS registration - likely to have high completeness • Infusion costs However: • Certain treatment waning scenarios cannot be tested within the time allowed for managed access • Quality of life data is being collected (trial and observational data); this could also be resolved through clinical expert input

***Summary based on full managed access proposal and Feasibility Assessment provided in committee papers**

- Appendix: Criteria applied by NICE committee

Managed access: Questions to committee

- Is donanemab plausibly cost-effective?
- Would managed access resolve all of the committee's uncertainties?
- Are any uncertainties not addressed by the proposal but sufficiently addressed elsewhere in the appraisal (e.g. at previous committee meetings or in the Draft Guidance)?
- Are any changes needed to the managed access proposal?
  - would the proposal require long-term RWE data collection across the NHS to adequately resolve your uncertainties?
  - Are any items unnecessary?
- Can/should uncertainty be mitigated 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

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Key questions for 3rd committee meeting

Issue	Questions	Slide links
Long term treatment effect assumptions	Are the company's long-term treatment assumptions reasonable? What is the committee's preferred approach?	11-12
Caregiver utilities	Are the company's caregiver utility values reasonable? What is the committee's preferred approach?	13–15
Health state occupancy at start of model: new issue	Are the company's updated assumptions reasonable?	16
Infusion cost	Which infusion cost estimate does the committee prefer to use in the modelling?	17–18

Thank you

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

RECAP from ACM1

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

RECAP from ACM1

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

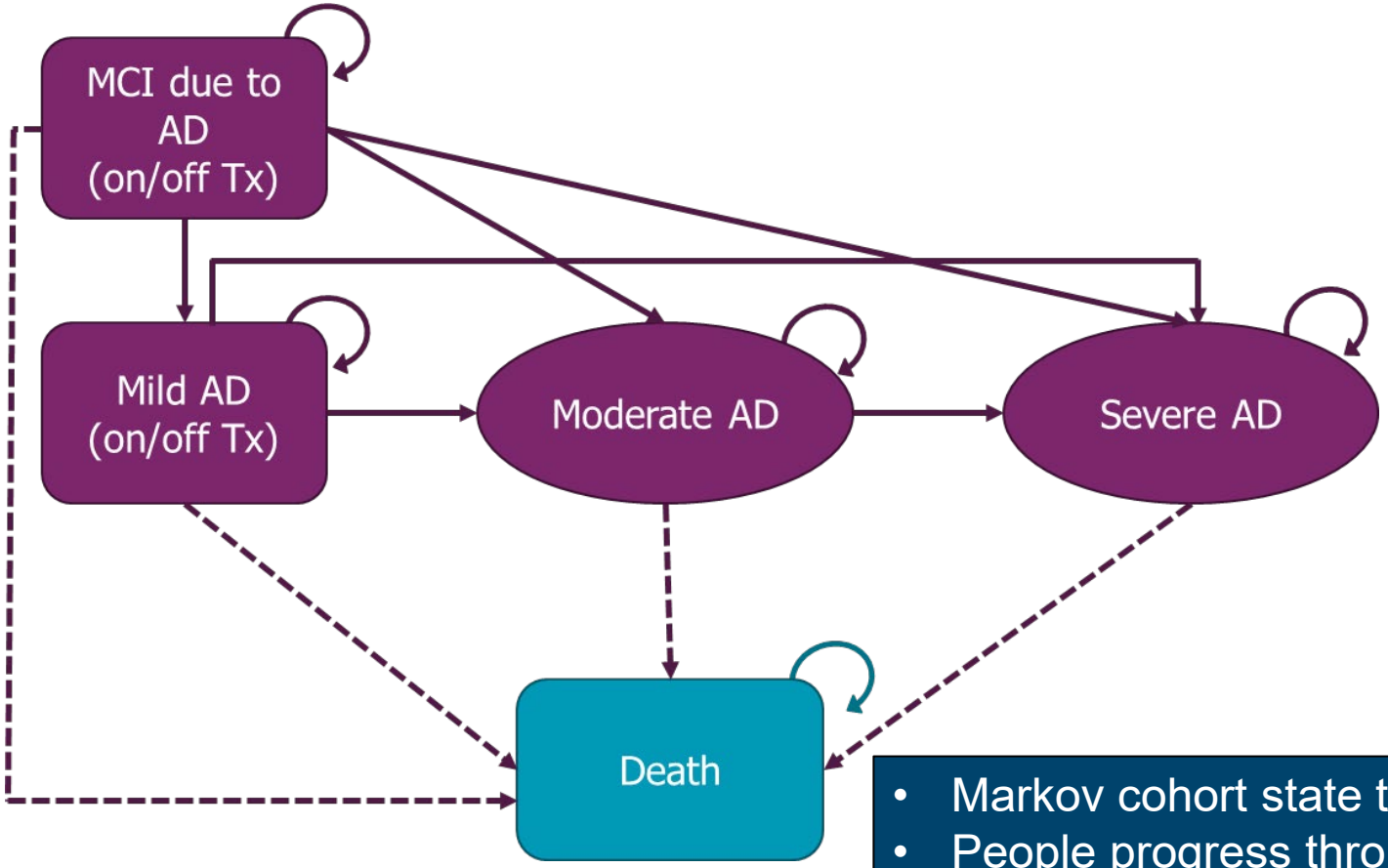
Trial	TRAILBLAZER-ALZ 2 (TB-AZL 2)	TRAILBLAZER-ALZ (TB-ALZ)
Design	Phase 3, randomised, double-blind	Phase 2, randomised, double-blind
Population	Adults with early symptomatic AD	Adults with early symptomatic AD
Comparison	Donanemab vs placebo	Donanemab vs placebo
Duration	18 months*	18 months*
Primary 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)

RECAP from ACM1

Company's model overview

The company developed a Markov model



Donanemab (Kisunla, Eli Lilly & Co):

- Marketing authorisation (MA) granted October 2024
- ACM1 held before final MA known, so committee considered full TB-ALZ 2 trial population, including APOE4 homozygotes
- Company updated population line with MA granted for ACM2
  - This included that donanemab is stopped on progression to moderate AD

- 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

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

RECAP from ACM2

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

RECAP from ACM2

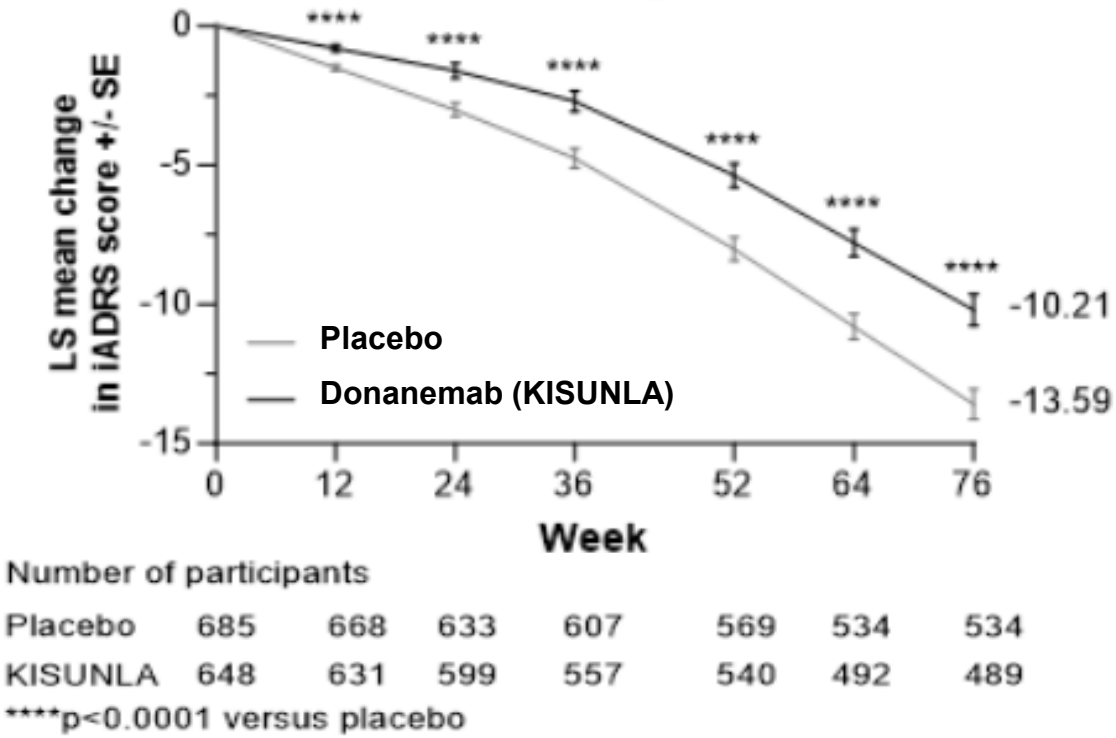
Clinical effectiveness in indicated population*, from Summary of Product Characteristics (*excludes APOE4 homozygotes)

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

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

Back to main deck: Summary of consultation responses

Consultation responses (1) – patient and professional orgs

Alzheimer's Research UK:

- Ongoing review of long-term data on donanemab needed – company has extensive TRAILBLAZER study plans. Valuable for finding to be incorporated into NICE's evaluation of donanemab long-term efficacy
- Infusion costs uncertain with large difference between company and NHSE – managed access could help resolve this. 3 clinicians estimated donanemab infusion costs to be £250 to < £500
- Impact on carers: true impact on carer QoL not being incorporated – committee notes significant uncertainty remains. Would like to understand the criteria NICE used to assess how appropriate a measure this is in reflecting the impact on carers for people with AD
- Unpaid care: much of costs of dementia fall on unpaid carers – consider significant cost of informal care is being neglected. Potential to apply a non-reference case approach to more accurately reflect costs?
- Concern that donanemab not eligible for the severity modifier
- Managed access: potential to help determine overall costs of treatment in real world setting, insight into long-term efficacy, impact on patient and carer QoL. Broader insights for AD research, system preparation for wider use of treatments in pipeline and improve lives of those affected by AD
    - Obstacles in infrastructure or AD registries must be address proactively for system readiness

Abbreviations: AD, Alzheimer's disease; NHSE, NHS England; QoL, quality of life

Back to main deck: Summary of consultation responses

Consultation responses (2) – patient and professional orgs

Alzheimer's Society:

- Respect NICE's recommendation but recognises disappointment that many people will have experienced
- Welcome second DG consultation and holding ACM3 to consider additional data. Appreciates rigour and flexibility demonstrated by NICE in appraisals of the first disease-modifying treatments for AD
- Encourage monitoring of longer-term data and real-world evidence by NICE

UK Clinical Pharmacy Association – Neurosciences Committee:

- Acknowledged relatively moderate gains compared to risk and burden and considered whether investment more beneficial if directed to improving pathways and care for all, rather than eligible patients only
- APOE4 testing: need for more clarity and care pathways that includes support for patients and families
- People with Down syndrome, young onset dementia and some ethnic groups not adequately represented in the trials – an issue that is a widespread issue across healthcare research
- Commissioning should determine resource allocation across diagnosis, treatment and cessation
- Encouraged real-world data collection through partnerships to allow pathway modifications if needed
- Burden for infusion unit – many are already at full capacity so might struggle; also outpatient capacity
- Additional training might be necessary for neurology, psychiatry, and geriatric medicine clinics

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4

Back to main deck: Summary of consultation responses

Consultation responses (3) – patient and professional orgs

Association of British Neurologists:

- Biomarkers: CSF should be considered part of standard of care diagnosis. But only recommended by NG97 if diagnosis can't be made using clinical assessment and brain scan. Biomarkers are not routinely offered in memory services at present. Unclear whether use of blood biomarkers in whole population to reduce CSF/PET use would be cost-saving overall. Further research on real world use in UK memory clinic population would be useful
- Best real-world data to indicate the likely proportions of MCI-AD versus mild-AD probably comes from national audit of diagnoses in memory services: 2019, 17% MCI, 67% dementia; 2023, 17% MCI, 71% dementia. Based on identifying any type of dementia (not specific to AD); 42% of cases estimated to be Alzheimer's pathology. No increase in diagnosis of MCI from 2019 to 2023, although many neurologists believe there will be shift to earlier presentation as public awareness of potential DMTs grows
- Impact on carers: concerns about face validity of carer utilities (EAG's GERAS) – virtually identical in MCI, mild AD, and moderate AD. By definition, patients with MCI have normal activities of daily living, whereas those with dementia need assistance. Burden on carers increases as dementia starts and progresses
- Managed access: potential to provide invaluable information about implementation of these new therapies in a real-world setting. Possible if carried out in selected specialist centres where the capabilities to safely deliver immunotherapies already present. Could both to provide evidence needed on cost-effectiveness and long-term treatment benefit, and help develop NHS DMT treatment pathway

Abbreviations: AD, Alzheimer's disease; DMT, disease-modifying therapy; EAG, evidence assessment group; MCI, mild cognitive impairment

Consultation responses (4) – others

Dementia Research Centre, UCL:

- Most people eligible to start treatment would be very likely have a partner or care-giver living with them
- Diagnosis stage: Individuals (and families) present later in disease when they think little can be done in slowing progression. This is already changing and is likely to increase the proportion of people seeking advice at an MCI stage. The availability of blood tests (plasma ptau217 is now available) could speed up time needed to determine amyloid positivity and eligibility – this would also increase the proportion who are at an MCI-AD stage (vs mild AD stage) compared to estimates derived from current memory service surveys/data. A managed access scheme may well also use a fast track screening approach to reduce the time to diagnosis for those who might be eligible.
- Carers: utility scores from GERAS study seem far from my own clinical experience having discussed with many carers their concerns and distress and burden when caring for someone with dementia
    - 3 of 5 domains in the EQ-5D: mobility, self-care, and usual activities have little bearing on what the carers of my patients describe as the impact of caring
    - QoL impacts reported by carers where their life partner / spouse has mild or severe dementia are consistently much lower than the numbers presented at the meeting (0.86 falling to 0.75)
    - A survey of 254 attendees at Alzheimer's Research UK Conference (2025) who were asked to estimate their QoL (where 100 = perfect health) if their partner or spouse had AD reported mean QoL rating of 57.5 for mild dementia and 26.9 for severe dementia (manuscript in preparation)

Abbreviations: AD, Alzheimer's disease; EQ-5D, EuroQol-5 domains; MCI, mild cognitive impairment; QoL, quality of life

Back to main deck: Summary of consultation responses

Consultation responses (5) – summary of web comments

"Negative recommendation is suitable" – 1 response

- Insufficient benefits were demonstrated in clinical trials
- If NICE approve for use in future, vital that a suitable funding variation is in place to ensure system readiness
- Need to work with NHSE to ensure that an implementation plan and associated funding are agreed and in place before publishing a positive TA. This is needed to ensure patient expectations are managed, and that a consistent approach is taken to implementing NICE guidance to avoid and variation in access to treatment and increasing health inequalities
- Significant concerns about high degree of uncertainties in both clinical evidence and economic modelling and analysis. A negative recommendation needs to stay in place until these issues have been resolved
- Equality considerations would need to be considered as part of funding variation

No new Equality considerations raised

"Negative recommendation is not suitable" – 1 response

- This is a crucial turning point for Alzheimer's disease which has taken too long to arrive
- Treatment has proven to clear amyloid plaque from the brain and leading to a lack of cognitive decline
- Cost will go down when it is available in the NHS and at the same time it will save the NHS millions
- Makes comparison with NICE recommendation of cancer drugs where evidence is limited

Abbreviations: NHSE, NHS England, TA, technology appraisal

Hazard ratios for mortality by AD severity

RECAP from ACM2 (appendix)

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: ACM2, 2nd committee meeting; AD, Alzheimer's disease; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

Back to TB-ALZ 2 long-term extension data

External control arm used in TB-ALZ 2 long-term comparison

Assumes pattern of disease progression same as in TB-ALZ 2 placebo arm

- [redacted]
- [redacted]
- Company acknowledges [redacted]

Table: Demographic and baseline characteristics

Time since baseline	TB-ALZ 2 Placebo	[redacted]
Age, mean (SD)	[redacted]	[redacted]
Male, %	[redacted]	[redacted]
APOE4 non-carrier, %	[redacted]	[redacted]
MMSE, mean (SD)	[redacted]	[redacted]
ADAS-Cog13, mean (SD)	[redacted]	[redacted]
CDR-SB, mean (SD)	[redacted]	[redacted]

Figure: TB-ALZ 2 placebo vs [redacted]

[redacted]

EAG noted: [redacted]

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Abbreviations: AD, Alzheimer's disease; ADAS-Cog13, Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; [redacted]; APOE4, apolipoprotein E 4; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; ESS, effective sample size; MMSE, mini-mental state examination; N, number; PW, propensity weighting; SD, standard deviation; TB-ALZ 2, TRAILBLAZER-ALZ 2

Back to TB-ALZ 2 long-term extension data

Sensitivity analysis in patients with amyloid clearance at 6 months in TB-ALZ 2 long-term comparison

Provides 2.5 years off-treatment follow up after stopping donanemab early

- Figure shows treatment effect of donanemab up to Month 36 for this population that cleared early
- External control arm is [redacted]

Figure: Analysis of adjusted mean change in CDR-SB score

[redacted]

Differences in CDR-SB (95% CI):

- [redacted] between **donanemab** and external control arm at 6 months,
- [redacted] between **donanemab** and external control arm at 18 months,
- [redacted] between **donanemab** and external control arm at 36 months

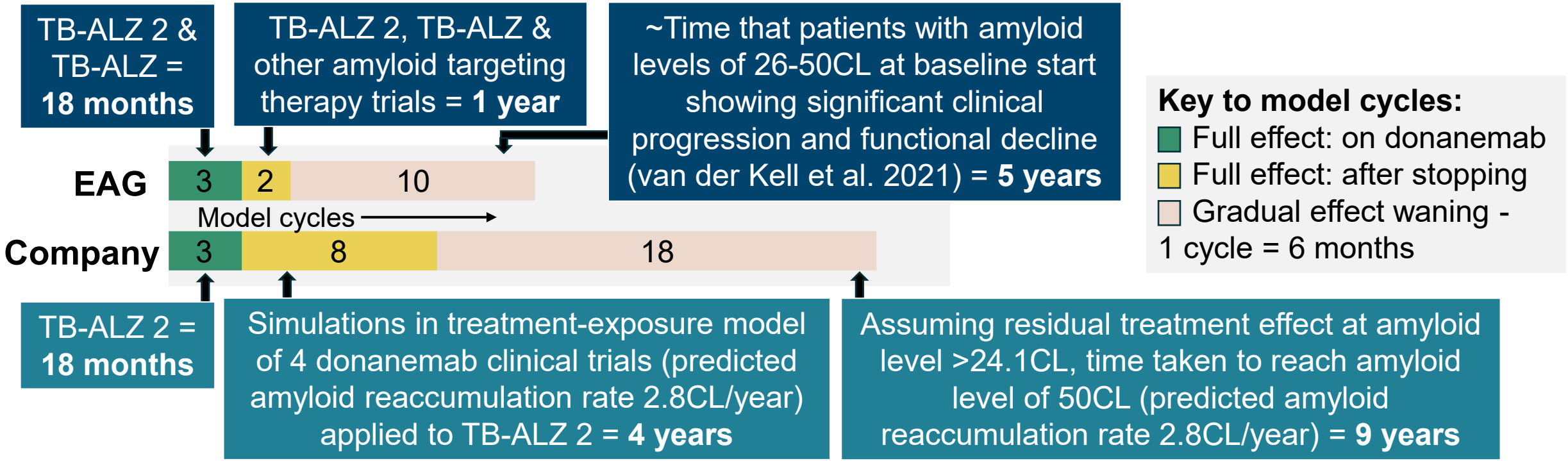
Abbreviations: [redacted] CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; TB-ALZ 2, TRAILBLAZER-ALZ 2

RECAP from ACM2

Long-term treatment effect assumptions at ACM2

Company and EAG disagree on modelled treatment effect duration and waning

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



Abbreviations: ACM2, 2nd committee meeting; CL, centiloids; EAG, evidence assessment group; TB-ALZ (2), TRAILBLAZER-ALZ (2)

Back to: Summary of company and EAG base case differences

RECAP from ACM2

Patient utility values

Company and EAG approaches unchanged, but company provided late re-analysis

Table: Patient utility values (proxy reported) presented at 1st committee meeting

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

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Abbreviations: ACM2, 2nd committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; MCI, mild cognitive impairment; MMSE, mini mental state exam

Back to main deck: Key issue: Caregiver utilities

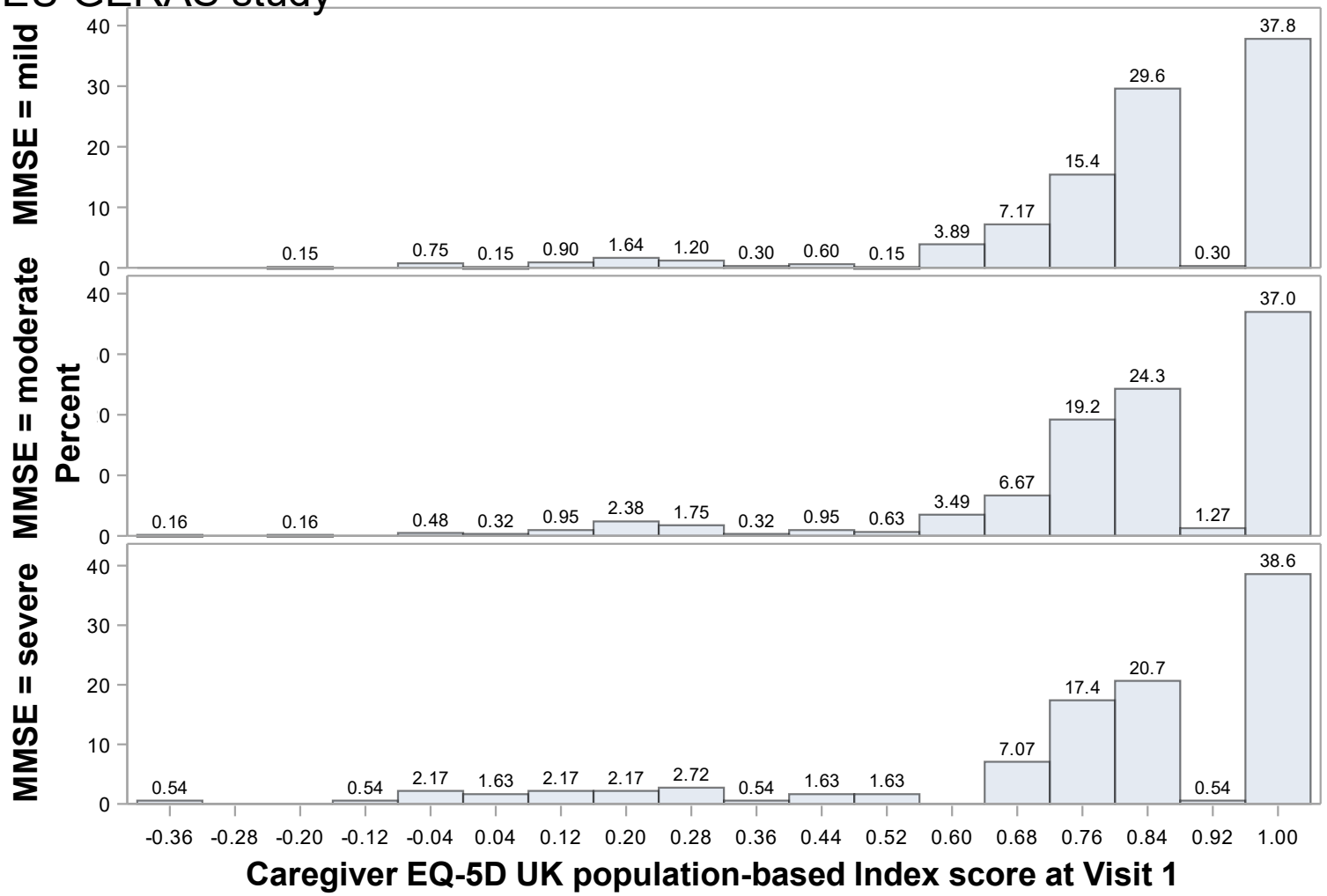
Psychometric properties of EQ-5D for caregiver utilities

Company: EQ-5D UK utility values of carers for people with AD lack sensitivity

Company response to draft guidance 2:

- A range of 37.0–38.6% of caregivers in community setting reported to be in perfect health consistently across disease states, which at face value does not appear to be plausible
- Proportion of caregivers reporting perfect health and consistency of distribution of response scores across disease states, suggest both a lack of responsiveness to different health states being assessed by the EQ-5D and a ceiling effect

Figure: Caregiver EQ-5D UK utilities by AD severity from the overall EU GERAS study



Abbreviations: ACM1, 1st committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; MCI, mild cognitive impairment

Back to main deck: Caregiver utility values used in base cases

EAG scenario based on company vignettes

EAG scenario provides values between those of company and EAG bases cases

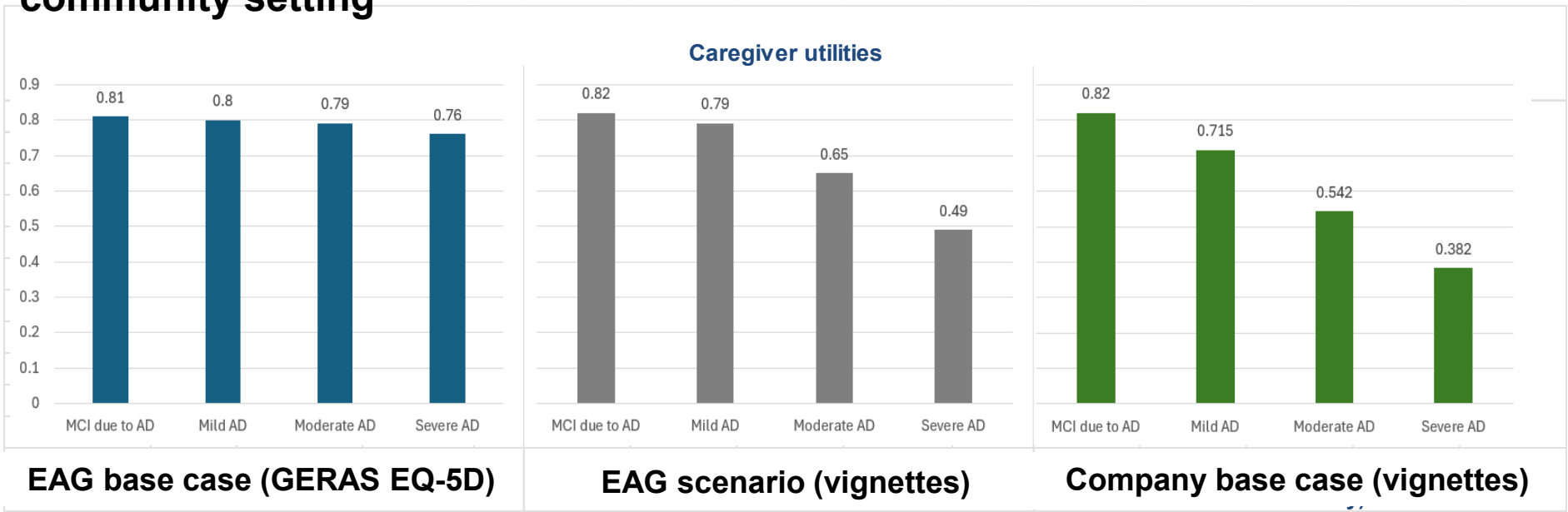
Table: Caregiver utilities in EAG scenarios based on company's vignettes – presented at ACM1

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

Company response to draft guidance 2:

- A key scenario analysis is presented using the EAG's scenario based on the company vignettes

Figure: Comparison of caregiver utility scenarios for **spouse caregiver, living in community setting**



Abbreviations: ACM1, 1st committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; MCI, mild cognitive impairment

Back to main deck: Key issue: Caregiver utilities

RECAP from ACM2

Key issue: Caregiver utilities

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

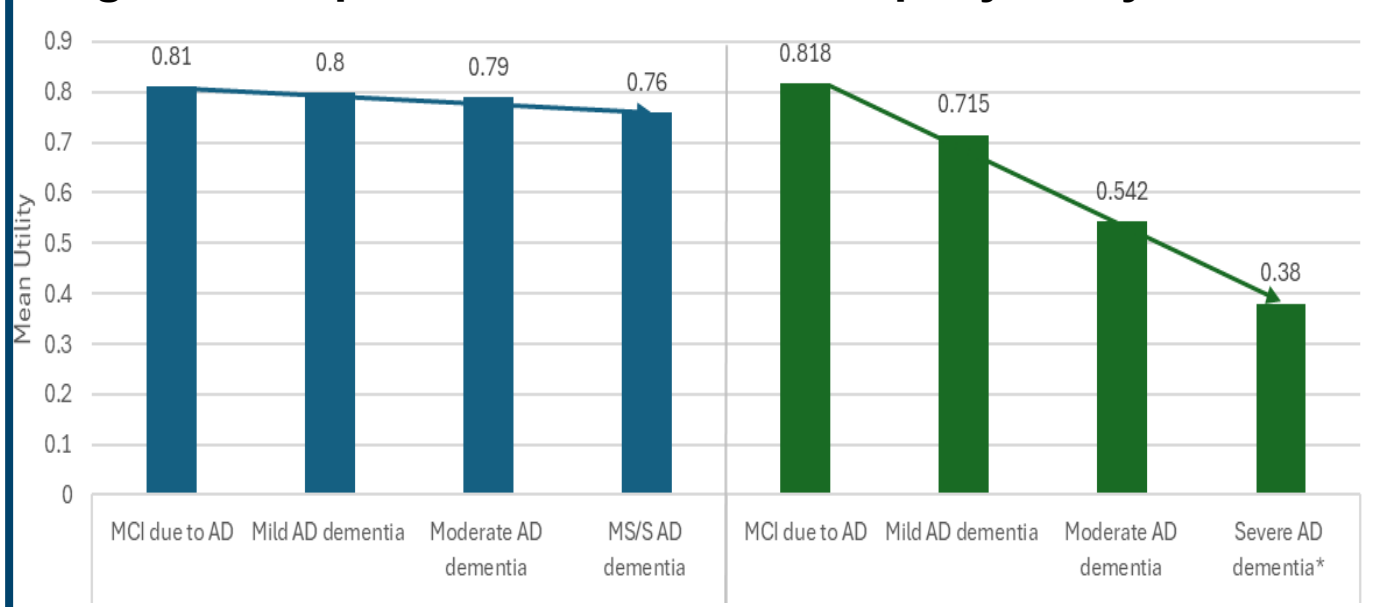
Committee at ACM1

- 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: Caregiver utility values

Figure: Comparison of EAG and company utility values



Abbreviations: ACM2, 2nd committee meeting; AD, Alzheimer's disease; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; MCI, mild cognitive impairment

Back to main deck: Key issue: Caregiver utilities

RECAP from ACM2

Key issue: Caregiver utilities

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

Company

- **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 not NICE reference case, as 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: ACM2, 2nd committee meeting; EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; ICER incremental cost-effectiveness ratio; QALY, quality-adjusted life year

RECAP from ACM2

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?

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Abbreviations: ACM2, 2nd committee meeting; 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

Back to main deck: Key issue: infusion costs – company and NHSE

RECAP from ACM2

Infusion costs: company, EAG and NHSE

Difference in costs estimated by the company and NHS England

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

Company: **£208**

- As in ACM1, uses £207.59 (SB12Z Deliver of Simple Parenteral Chemotherapy)
- NHSE cost represents a considerable overestimation of the administration costs

NHSE: **Updated: £432**

- Updated approach for ACM2
- 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)
- Costing is consistent with lecanemab appraisal

EAG **Aligns with NHSE**

- Uses revised NHSE cost (£432)
- Applying company cost has moderate impact on reducing EAG ICER (ACM2)

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

Back to main deck: Key issue: infusion costs – company and NHSE

Infusion costs: NHSE process for estimating costs

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

Back to main deck: EAG scenarios

Cost-effectiveness results: company scenarios

All company scenarios are above £20,000/QALY

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

No.	Scenario (applied to revised company base case)	ICER (£/QALY)
Company updated base case		£27,366
1	Caregiver utility: EAG scenario approach to using company's vignette study	£29,888
2	Caregiver utility: Using GERAS EQ-5D as source (EAG preferred)	£40,754
3	Caregiver utility: Excluding any caregiver utilities from base case	£43,197
4	IV infusion cost: Neurology consultant-led outpatient, first attendance (£222.91)	£27,749
5	IV infusion cost: SB13Z Delivery of Complex Parenteral Chemotherapy (£256.95)	£28,600
6	Including unpaid care costs	£21,082

Abbreviations: EAG, evidence assessment group; EQ-5D, EuroQol-5 domains; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PAS, patient access scheme; QALY, quality-adjusted life year

RECAP from ACM1 (appendix)

QALY weightings for severity

Severity modifier calculations and components:

QALYs people without the condition (A)

QALYs people with the condition (B)

Health lost by people with the condition:

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

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

Table: QALY shortfall calculations for MCI and mild AD dementia

Base case	QALYs without condition	QALYs with condition	Absolute QALY shortfall	Proportional QALY shortfall
Company updated*	8.04	4.09	3.95	49.15%
EAG	8.04	3.82	4.22	52.51%

*At clarification (question B33), the company acknowledged that donanemab **does not meet the criteria** for a severity modifier, so this was excluded from the updated company base case. (Reference: DSU Technical support document 23 [Wailoo 2024])

NICE

Abbreviations: ACM1, 1st committee meeting; DSU, decision support unit; QALY, quality-adjusted life year

Back to main deck: Summary of company and EAG base case differences

No further issues raised during second draft guidance consultation

Equality considerations – ACM1 and ACM2 summary

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"

NICE

Abbreviations: ACM1/2, 1st/2nd committee meeting; AD, Alzheimer's disease; MMSE, mini metal sate examination

Back to main deck: Summary of company and EAG base case differences

No further aspects raised during second draft guidance consultation

Aspects not captured in modelling – ACM1 and ACM2 summary

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

NICE

Abbreviations: ACM1/2, 1st/2nd committee meeting; AD, Alzheimer's disease; APOE4, apolipoprotein E 4; IV, intravenous; MRI, magnetic resonance imaging; 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**