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

For committee – contains redacted [redacted] information

Technology appraisal committee D [3 July 2024]

Chair: Megan John

Lead team: Andy Fox, Carole Pitkeathley, Will Sullivan

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

NICE National Institute for Health and Care Excellence

Background on Alzheimer's disease

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

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

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

- Alzheimer's is thought to be caused by abnormal build-up of proteins in the brain (such as beta-amyloid) → amyloid deposits form plaques and disrupt the function of brain cells

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

Background on Alzheimer's disease

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

- NIA-AA guidelines are 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**

- However, the presence of biomarker (ie beta-amyloid) is needed to confirm Alzheimer's disease [Note: the different terminology used during diagnosis can be confusing]
- Apolipoprotein E-4 (APOE-4) gene increases an individual's risk for developing Alzheimer's disease

Note: for brevity, in subsequent slides 'MCI due to AD' is generally shortened to MCI and 'mild AD dementia' is generally shortened to mild AD

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

Patient perspectives*

Alzheimer's is life-limiting for patients and carers

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

- Alzheimer's disease is progressive and life-limiting, there is no cure
- For many, a diagnosis instils fear and confusion, impacting the individual with the diagnosis and those involved in their care, as well as their broader family and friends
- Easy for family carers to become socially isolated as they put their own lives on hold, often experiencing a severe deterioration in their own health and wellbeing
- 39% of carers provide 100+ hours of care a week, 112,540 working age carers no longer in work, 147,000+ working less due to caring

"'When you've met 1 person with Alzheimer's disease, you've met 1 person with Alzheimer's disease'…reflects the risk of making general assumptions on what it's like to live with the disease"

*Includes responses to some organisations' surveys conducted for the appraisal of another DMT, lecanemab, where the organisations consider they also apply to donanemab

Abbreviations: DMT, disease-modifying therapy; MRI, Magnetic resonance imaging; PET, positron emission tomography

Patient perspectives*

Alzheimer's is life-limiting for patients and carers

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

- Most cited advantage of treatment such as donanemab expected to be slowing the progression of disease
- These drugs may work best when used as early as possible
- 1 patient identified as having donanemab in a trial extension phase

> "I don't seem to be slipping down that terrifying slope into dementia… [My wife] has seen a deterioration in me, [but] I don't"

- Concerns with donanemab include difficulties during infusion, medical equipment and staff expertise, experiences with MRI and PET scans, safety and effectiveness

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

*Includes responses to some organisations' surveys conducted for the appraisal of another DMT, lecanemab, where the organisations consider they also apply to donanemab

Abbreviations: DMT, disease-modifying therapy; MRI, Magnetic resonance imaging; PET, positron emission tomography

Patient perspectives*

Donanemab offers hope, but must be an informed decision about advantages and disadvantages

Direct quotes from patients and carers

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

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

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

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

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

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

*Includes responses to some organisations' surveys conducted for the appraisal of another DMT, lecanemab, where the organisations consider they also apply to donanemab

Clinical perspectives

Donanemab potentially addresses significant unmet need but there are challenges

Submissions from FPH, ABN, RCP, NHSE, UCL Dementia Research Centre

- AD is a progressive disease with underlying pathology that starts at least 10 years before symptoms, it is complex, and our understanding is incomplete
- Current treatments for AD are limited, leading to small, symptomatic benefits for some patients, but do not target specific aspects of AD
- Meaningful treatments in early AD would prevent or significantly delay progression
- But no consensus and differing views on minimum clinically important difference in endpoints used in trials

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

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

Clinical perspectives

Donanemab potentially addresses significant unmet need but there are challenges

Submissions from FPH, ABN, RCP, NHSE, UCL Dementia Research Centre

- Window for [donanemab] is limited – timely diagnosis is much more important than with current treatments
- High uncertainty in longer term cumulative benefits on clinically relevant outcomes
- Donanemab could represent a clear shift in managing dementia, leading to a range of benefits, but there are potential significant challenges:
  - How to optimise and tailor use in clinical practice – for selective and targeted use
  - Access to and use of biomarkers, including diagnostic accuracy concerns
  - Variations in diagnostic terminology (6+ ways to describe the same people)
  - System readiness: lack of commissioned care pathways, staff training and expertise, limited capacity and infrastructure, increased costs
  - NHSE: need for substantial staffing, training and infrastructure investment

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

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 from 50% to 90%
- People with more agency and resources will 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

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

Equality considerations

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

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 donanemab trial due to age cut-off for inclusion 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"

Abbreviations: AD, Alzheimer's disease

Key issues for committee discussion

	Issue (EAG report key issue number)	ICER impact
Clinical-effectiveness	Use of acetylcholinesterase inhibitors and memantine (1) – see appendix for consideration of this issue	Minimal
	Outcome measure used for treatment effect (2)	Moderate (scenario)
	Analysis of clinical effectiveness results (3)	Unknown
	Potential impact of risk of bias in trials (4)	Small (for base case)
	Impact of APOE-4 allele status (5)	Unknown
Cost-effectiveness	Hazard ratios for mortality by Alzheimer's disease severity (6)	**Large**
	Long term treatment effect assumptions (7)	**Large**
	Patient utility values (8)	Small
	Carer utility values (9)	**Large**
Others	Modelled costs: company, EAG and NHSE	**Large** (NHSE)

Abbreviations: APOE-4, apolipoprotein E 4; EAG, evidence assessment group; NHSE, NHS England;

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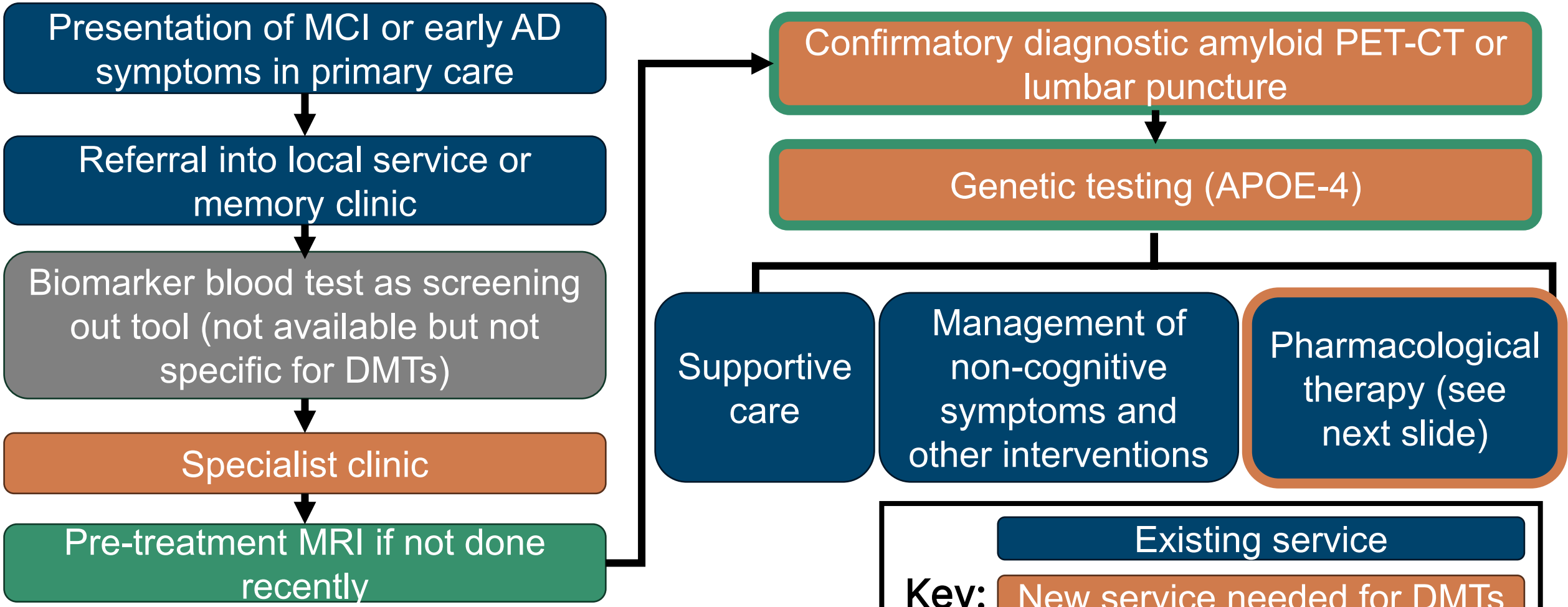
Diagnostic pathway

NHSE proposed diagnostic pathway – new elements needed for DMTs highlighted



Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein E 4; CT, computed tomography; DMT, disease modifying treatment; MCI, mild cognitive impairment; MRI, Magnetic resonance imaging; NHSE, NHS England; PET-CT, positron emission tomography-computed tomography

Treatment pathway

Current treatment pathway with new treatments highlighted

Current treatments for each AD stage plus proposed positioning of donanemab

Mild cognitive impairment

- Donanemab

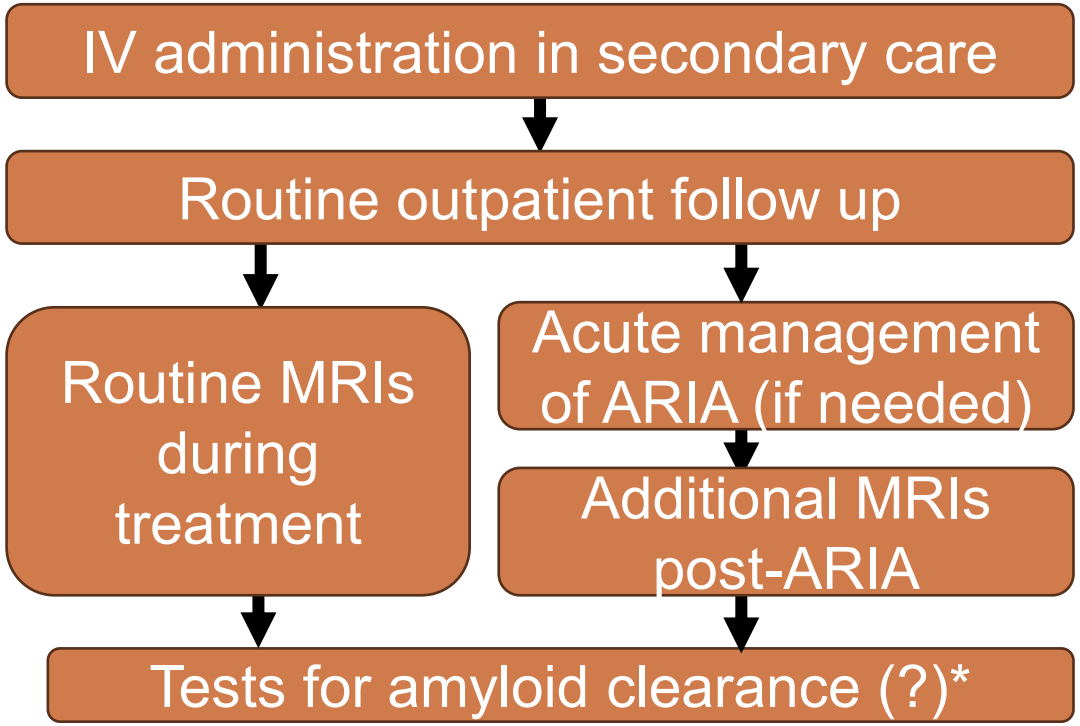
Mild AD

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

Moderate to severe AD

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

Treatment pathway needed for donanemab



*Involves new requirement for amyloid radiotracer supply – see appendix slide on Radiotracer use in PET

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

Donanemab ([redacted], Eli Lilly and Co)

Marketing authorisation	• Not yet been granted marketing authorisation by the MHRA • Anticipated indication wording: [redacted]
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, which slows down AD progression
Administration	• Intravenous infusion over at least 30 minutes. After infusion, patients should be observed for at least 30 minutes • Recommended 700mg Q4W for first 3 doses, then 1,400mg Q4W per dose • Treatment should be continued until amyloid plaques are cleared as confirmed using a validated method **up to a maximum of 18 months**
Price	• List price [redacted] per 350mg pack (x2 for 700mg, x4 for 1,400mg) • List price for 18 months of treatment = [redacted] • Patient access scheme applies

Abbreviations: AD, Alzheimer's disease; MIC, mild cognitive impairment; MHRA, Medicines and Healthcare products Regulatory Agency; Q4W, every 4 weeks

See appendix – TB-ALZ 2 Summary of baseline characteristics

Key clinical trials

TRAILBLAZER-ALZ 2 is the pivotal phase 3 trial of donanemab used in the model

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
Intervention	Donanemab	Donanemab
Comparator	Placebo	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)
Used in model?	Yes, used in model	No – see related EAG Key issue

*Data from TB-ALZ 2 long-term extension expected late 2024, giving extra 18 months follow-up

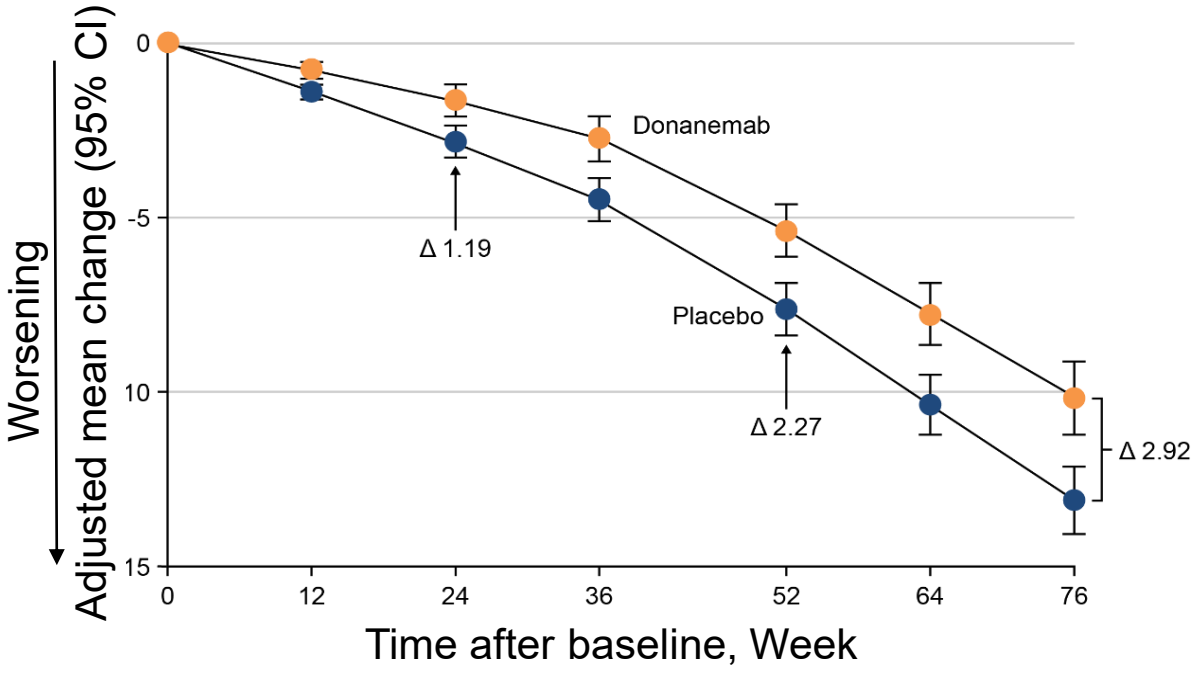
Abbreviations: AD, Alzheimer's disease; ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale–Cognitive; ADCS-iADL, Alzheimer's disease cooperative study-activities of daily living; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, integrated Alzheimer's disease rating scale; MMSE, mini-metal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

See appendix – outcome measures and clinically important differences

Key clinical trial results from TRAILBLAZER-ALZ 2

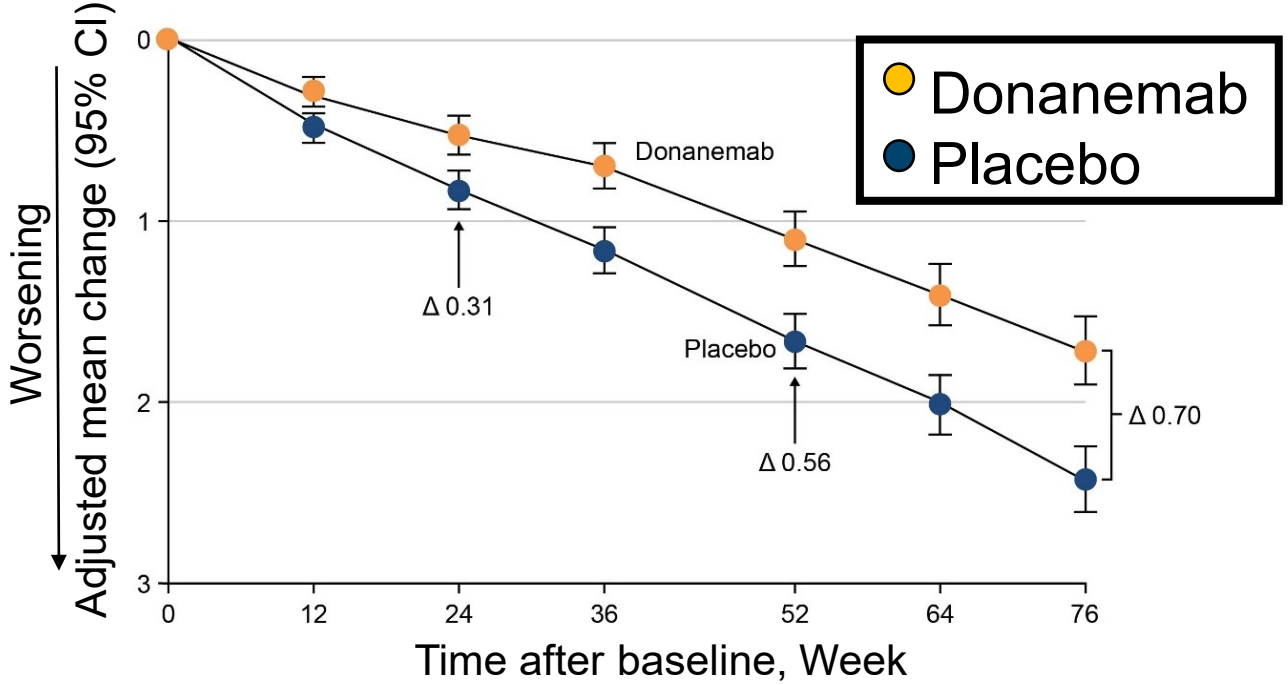
Donanemab reduces decline in iADRS and CDR-SB score over 18 months

Figure: iADRS change from baseline to 76 weeks (NCS2 analysis), mITT population



- Disease progression delayed by 1.4 months (95% CI 0.5, 2.3) at 76 weeks on iADRS score, donanemab compared with placebo

Figure: CDR-SB change from baseline to 76 weeks (MMRM analysis), mITT population



- Disease progression delayed by 5.4 months (95% CI 3.9, 7.0) at 76 weeks on CDR-SB score, donanemab compared with placebo

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Abbreviations: See slides notes

See appendix – outcome measures and clinically important differences

Key clinical trial results from TRAILBLAZER-ALZ 2

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

Table: TB-ALZ 2 primary and key secondary outcome at 18 months – mITT population

Outcome	iADRS		CDR-SB	
Treatment arm	Donanemab	Placebo	Donanemab	Placebo
N at Baseline, Week 76	775, 583	824, 653	794, 598	838, 672
Natural cubic spline with 2 degrees of freedom (NCS2) analysis				
LS mean change, Baseline to Wk 76	-10.19	-13.11	1.66	2.33
LS mean treatment difference at Wk 76 (95% CI) [p-value]	2.92 (1.51 to 4.33) [<0.001]		-0.67 (-0.92, -0.43) [<0.001]	
Progression slowed vs placebo, %	22.3%		28.9%	
Mixed models for repeated measures (MMRM) analysis				
LS mean change, Baseline to Wk 76	-10.19	-13.22	1.72	2.42
LS mean treatment difference at Wk 76 (95% CI) [p-value]	3.03 (1.60 to 4.47) [<0.001]		-0.70 (-0.95, -0.45) [<0.001]	
Progression slowed vs placebo, %	22.9%		28.9%	

- iADRS worsening = decrease in score (negative change)
- CDR-SB worsening = increase in score (positive change)

Abbreviations: See slides notes

See appendix – outcome measures and clinically important differences

Moderate ICER impact (scenario)

Key issue: Outcome measure used for treatment effect

Company and EAG agree on using CDR-SB, but using iADRS increased ICER

Company

- Donanemab treatment effect uses key secondary outcome of TB-ALZ 2, CDR-SB
- At clarification, company explored impact of using primary outcome, iADRS
  - Using iADRS for treatment effect increased company ICER from £19,736 to £34,074

Table: TB-ALZ 2 trial HR for progression

Measure	HR (95% CI)	In model?
CDR-SB	0.62 (0.52 to 0.75)	Base case
iADRS	0.70 (0.58 to 0.84)	Scenario

EAG comments

EMA guidance (2018):

- No ideal tool for assessing efficacy of treatments for dementia
- Range of tools may be needed
- Approach may vary for early AD vs established disease

RCPsych and ABN comments

- No consensus on 'best outcome' to measure treatment response
- AD does not have linear course and changes in earlier stages, especially over 18-month trial, may be less evident than in later stage of AD
- iADRS not well-established in clinical practice, so difficult to interpret numerical differences

Abbreviations: ABN, association of British Neurologists; AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CI, confidence interval; HR, hazard ratio; iADRS, Integrated Alzheimer's Disease Rating Scale; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; RCPsych, Royal College of Psychiatrists

See appendix – outcome measures and clinically important differences

Key issue: Outcome measure used for treatment effect

Company and EAG agree on using CDR-SB, but using iADRS increased ICER

Moderate ICER impact (scenario)

EAG comments continued

Clinical expert advice:

- MMSE is only measure used in clinical practice, useful to identify AD, but disease progression often not assessed. Other tools used only in clinical trials
- CDR-SB adequately reflects how cognition and function are assessed in clinical practice and captures factors important to those with AD and their caregivers

EAG preferred approach:

- On balance, CDR-SB appropriate to inform treatment effect, so used in EAG base case
- iADRS a less well-established than CDR-SB but there is value in considering iADRS
  - Scenario analysis of iADRS for treatment effect increased EAG base case by ~£40K
- EAG requested meta-analysis of TB-ALZ 2 and TB-ALZ trials to explore impact of outcome measure further – see next **Key issue**

Is the CDR-SB outcome measure (used in company and EAG modelling) suitable for decision making?

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; ICER, incremental cost-effectiveness ratio

Key issue: Analysis of clinical effectiveness results

Unknown ICER impact

EAG noted inconsistent results between trials, considers meta-analysis is needed

Company

- At clarification, presented sensitivity analyses of key clinical outcomes by imputation method – to explore the impact of using different methods to account for missing values
- Did not provide meta-analysis requested by EAG of TB-ALZ 2 and TB-ALZ trials for CDR-SB and iADRS outcomes, stating heterogeneity between studies would limit feasibility and validity

EAG comments

- Company suggests that slowing of AD progression by >20% is clinically meaningful
  - This benchmark was met in donanemab trials (see next slide)
- European consensus is that slowing of progression by 30–50% is clinically meaningful

Result of subgroup analysis for baseline AD severity:

- Treatment difference numerically smaller for MCI subgroup compared with mild AD dementia subgroup, although MCI had smaller sample size so results more uncertain
- % progression slowed: higher for MCI on iADRS, very similar to mild AD on CDR-SB

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

Key issue: Analysis of clinical effectiveness results

Unknown ICER impact

EAG noted inconsistent results between trials, maintains meta-analysis is needed

EAG comments continued

- In overall population, CDR-SB treatment difference larger in TB-ALZ 2 trial (modelled) than in TB-ALZ, but opposite seen for iADRS measure

Table: TB-ALZ 2 and TB-ALZ trials key efficacy analyses – mITT population

Trial and outcome	CDR-SB		iADRS	
	Donanemab	Placebo	Donanemab	Placebo
TB-ALZ 2 trial: LS mean difference at Week 76 (95% CI) [p value]	-0.70 (-0.95, -0.45) [p<0.001]		2.92 (1.51 to 4.33) [p<0.001]	
• Progression slowed vs placebo, %	28.9%		22.3%	
TB-ALZ trial: LS mean difference at Week 76 (95% CI) [p value]	-0.36 (-0.83, 0.12) [p=0.139]		3.20 (0.12, 6.27) [p=0.04]	
• Progression slowed vs placebo, %	22.8%		31.8%	

- Higher ICER likely if CDR-SB results from TB-ALZ included in company's modelling
- EAG considers that meta-analysis of 2 trials needed to explore results further

Does the committee consider any other analyses are needed?

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; ICER, incremental cost-effectiveness ratio; LS, least squares; MCI, mild cognitive impairment; mITT, modified intent-to-treat

Key issue: Potential impact of risk of bias in trials

Small ICER impact (for base case)

Risk of bias leads to uncertainty in the treatment effect applied in the model

Table: Summary of risk of bias assessments of TB-ALZ 2 and TB-ALZ trials

Company assessment	EAG assessment
Outcome not stated	Outcome was CDR-SB at Week 76
Overall risk of bias: 'Some concerns'	Overall risk of bias: 'High risk'
'Some concerns': Potential for study unblinding due to occurrence of ARIA • Considered this to be performance bias – due to deviations from intended interventions	'High risk': Potential for study unblinding due to occurrence of ARIA and infusion-related reactions • Considered this to be detection bias – impact of unblinding on assessment of CDR-SB outcome • Acknowledged in published trial papers
'Low': • Attrition bias – due to missing outcome data. Impact explored in sensitivity analyses of outcomes by imputation method – see appendix	'Some concerns': • Attrition bias – due to missing outcome data. More people discontinued due to AEs with donanemab than with placebo and outcome may differ whether discontinued or not

Abbreviations: AD, Alzheimer's disease; AE, adverse event; ARIA, amyloid-related imaging abnormalities; CDR-SB; Clinical Dementia Rating scale Sum of Boxes

Key issue: Potential impact of risk of bias in trials

Risk of bias leads to uncertainty in the treatment effect applied in the model

Small ICER impact (for base case)

EAG comments

- Risk of bias due to potential unblinding with ARIA may be mitigated because CDR-SB raters were blinded to AE information
  - But CDR-SB is completed through interview with patients and carers – unclear how people were prevented from becoming aware of treatment assignment when AEs - this awareness could conceivably impact their CDR-SB responses
- Impact is uncertainty in accuracy of treatment effect on CDR-SB progression used in model – may be over- or under-estimated
- After clarification, company provided sensitivity analyses of key clinical outcomes with censoring for first ARIA and infusion-related reactions – see appendix. HRs for disease progression [redacted] for CDR-SB and [redacted] for iADRS vs original analysis
  - HR difference for CDR-SB not expected to meaningfully change ICER (base cases)
  - HR difference for iADRS increases ICER by approximately £30,000 (EAG scenario)

What are the committee's views on the potential risk of bias in TB-ALZ 2 trial? Does the committee consider any other analyses are needed to explore potential risk of bias?

Abbreviations: AD, Alzheimer's disease; AE, adverse event; ARIA, amyloid-related imaging abnormalities; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment

Unknown ICER impact

Key issue: Impact of APOE-4 allele status

Adverse reactions differ by allele status, some evidence efficacy also differs

Company

- APOE-4 is a known risk factor for ARIA-E
- Interaction test showed APOE-4 homozygous status not a treatment effect modifier

EAG comments

- APOE-4 allele increases ARIA risk (captured in model for TB-ALZ 2) – see Table
- 1 EAG clinical expert advised: people homozygous for APOE-4 should probably not be treated with donanemab due to ARIA risk; for people heterozygous, potential risks and benefits need to be clearly explained

Table: ARIA-E in donanemab arm

APOE-4 genotype	ARIA-E, % patients	
	TB-ALZ 2 (n=131)	Integrated dataset (n=2,727)
Non-carrier	11.1%	[redacted]
Heterozygote	30.0%	[redacted]
Homozygote	44.0%	[redacted]

Note: MHRA will consider benefit:risk balance of donanemab treatment in different groups, which may include APOE-4 allele status

Abbreviations: APOE-4, apolipoprotein E genotype e4 allele; ARIA-E, amyloid-related imaging abnormalities of oedema/effusions; MHRA, Medicines & Healthcare products Regulatory Agency

Key issue: Impact of APOE-4 allele status

Unknown ICER impact

Adverse reactions differ by allele status, some evidence efficacy also differs

EAG comments continued

- Subgroup analyses of TB-ALZ 2 hint at potential differences in response by APOE-4 status (not captured in model) – progression in homozygous crossed line of no effect

Table: Response to donanemab vs placebo at Week 76

APOE-4 genotype	iADRS		CDR-SB	
	Adjusted mean difference	Progression slowed vs placebo (95% CI)	Adjusted mean difference	Progression slowed vs placebo (95% CI)
Non-carrier	4.58	28.1% (12.2, 43.9)	-0.76	28.7% (11.3, 46.1)
Heterozygote	2.87	23.8% (7.9, 39.7)	-0.73	33.6% (18.1, 49.1)
Homozygote	1.01	9.3% (-21.8, 40.4)	-0.41	17.7% (-8.1, 43.6)

- Uncertainty due to low numbers e.g. n≤220 homozygous status in TB-ALZ 2
- Unclear if feasible to obtain HR for disease progression for homozygotes due to low numbers – clarification from company needed about whether this is possible

Are any further analyses needed to capture any difference in treatment effect by AOPE-4 mutation status?

Abbreviations: APOE-4, apolipoprotein E genotype e4 allele; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CI, confidence interval; HR, hazard ratio; iADRS, Integrated Alzheimer's Disease Rating Scale; vs, versus

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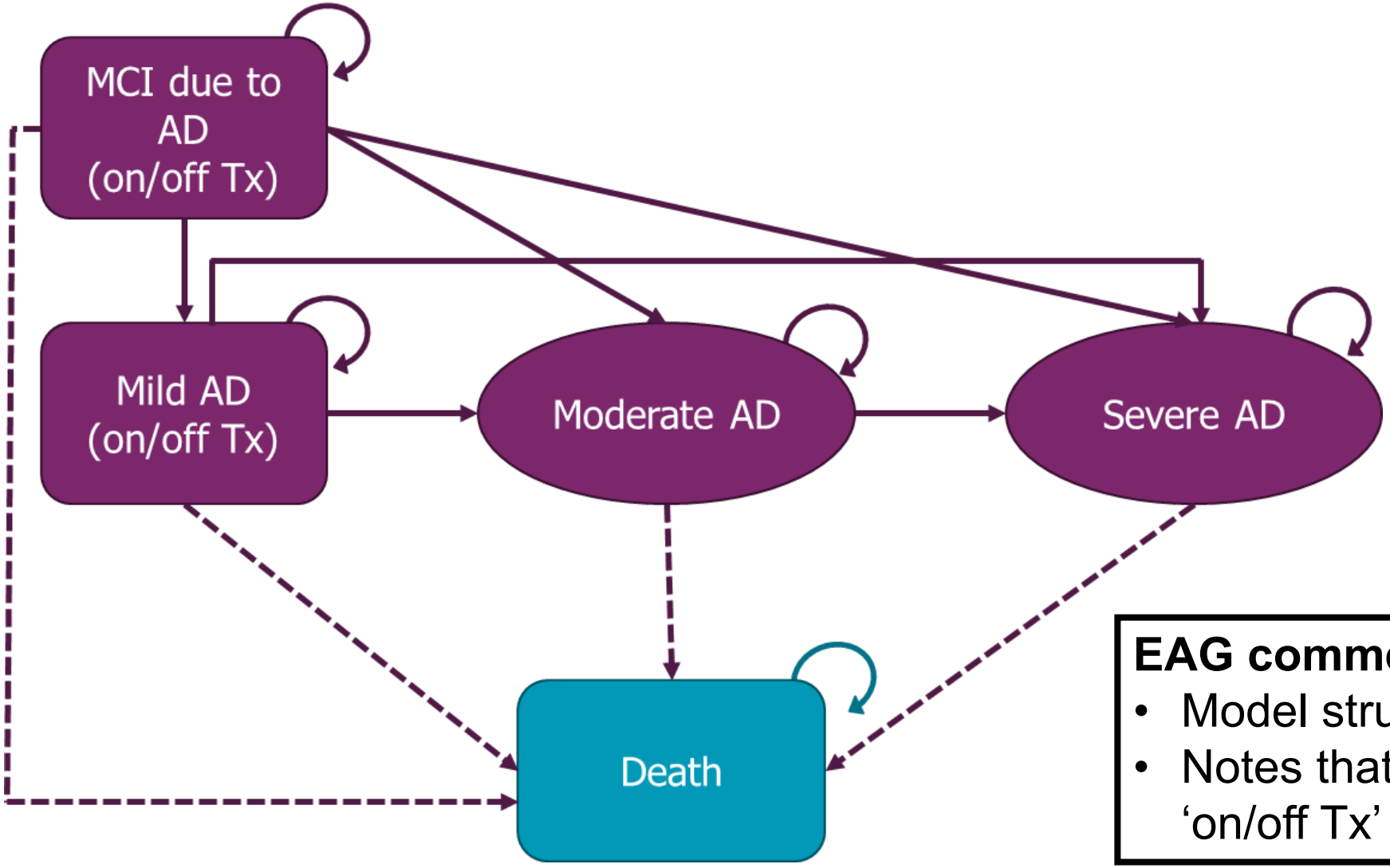
See appendix – How the technology affects costs and QALYs

Company's model overview

The company developed a Markov 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

EAG comments

- Model structure is appropriate
- Notes that patients could also be 'on/off Tx' in moderate AD health state

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; Tx, treatment

How company incorporated evidence into model

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

Input	Assumption and evidence source
Baseline inputs	TRAILBLAZER-ALZ 2 trial, 20.4% MCI due to AD and 79.6% mild AD dementia
Donanemab treatment effect	HR vs placebo on CDR-SB measure from TB-AZL 2 for MCI, mild AD or moderate AD
Treatment stopping	• 90% patients stop after a fixed duration of 18 months • 10% patients stop due to amyloid clearance at 6 or 12 months (PET scan) • If progressing to severe AD health state or due to an AE leading to discontinuation
Adverse events	• TB-AZL 2 for donanemab, ARIA applied in 1st cycle • Disutility: ARIA -0.14 (=headache, 72 days), anaphylactic reaction -0.112, 30 days)

Abbreviations: AD, Alzheimer's disease; AE, adverse event; ARIA, amyloid-related imaging abnormalities; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; MCI, mild cognitive impairment; HR, hazard ratio; PET, positron emission tomography;

How company incorporated evidence into model

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

Input	Assumption and evidence source
Transition probabilities	• US NACC dataset for CDR-SB-defined health states
Risk of residential care	• Spackman et al. 2012 (0% for MCI subgroup)
Patient utility	• Landeiro et al. (SLR and fixed-effects meta-analysis for all health states) for mild, moderate or severe AD; MCI = general population
Caregiver utility	• From 2 vignette studies, used time trade-off approach (1.8 caregivers/patient)
Health state unit costs	• Administration, diagnostic and monitoring costs are NHS costs for 2021/22. See slide on Modelled costs: company, EAG and NHSE • Annual costs of residential care from Jones et al. PSSRU report (£1,442 per week), with 49.7% categorised as 'direct medical costs' • MCI due to AD health state not in PSSRU report, so other published sources used (Wittenberg et al.)

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre; NHSE, NHS England; PSSRU, Personal Social Services Research Unit; SLR, systematic literature review

See appendix – Company's model: transition probabilities

Company's model: risk of residential care

EAG prefers to assume higher likelihood of residential care across AD severities

- Company used Spackman et al. 2012 values:

Table: Annual probability of residential care

Health state	Company model (Spackman et al.)	EAG preferred (GERAS, UK)
MCI	0%	-
Mild AD	1.2%	4.1%
Moderate AD	3.4%	8.5%
Severe AD	6.6%	10.5%

EAG comments

- 2 clinical experts considered values from GERAS study were more suitable, although 1 expert expected that 15-20% of people with severe AD move to residential care per year
- EAG prefers to use GERAS study which includes UK patients

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

Key issue: Hazard ratios for mortality by AD severity

Large ICER impact

Company assumes mortality risk is same in mild, moderate and severe AD

Company

- Base case applies single HR for mortality of 2.55 (compared with general population [=MCI]) for mild, moderate and severe AD to avoid adding uncertainty to model
  - Same HR applied for community and residential care setting
- Provided scenario for variable mortality by AD severity (US NACC data) – see appendix

EAG comments

- Mortality risk increases with AD severity
- Clinical experts: inconsistent views on whether MCI = general population mortality
- Company NACC data not plausible: point estimate of mortality in mild AD > moderate AD
- EAG prefers recent Crowell et al publication (AD mortality at age 80, based on NACC) to approximate mortality in model population with starting age 73 years – see next slide
  - Uses HRs for mortality of 2.4, 3.1 and 6.6 for mild, moderate and severe AD
  - EAG's mortality assumptions increased company ICER from £19,736 to £42,736
- Tested other sources (Ross et al and Lin et al) in scenario analyses

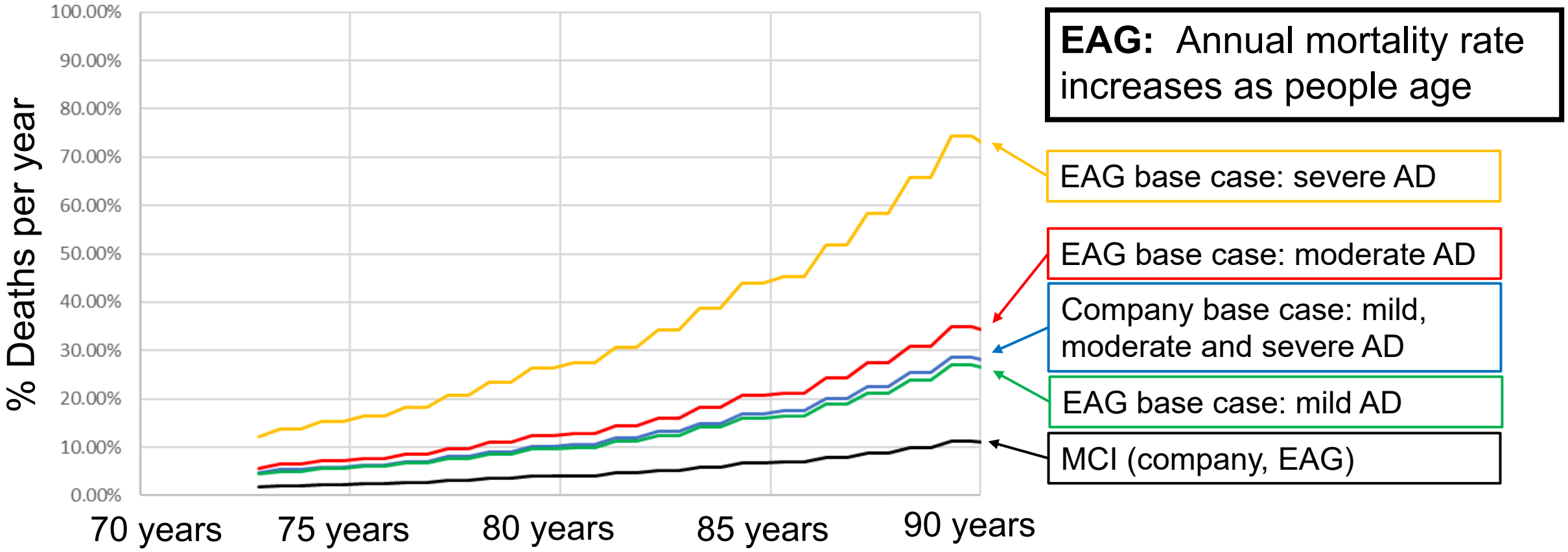
Abbreviations: AD, Alzheimer's disease; HR hazard ratio; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

Key issue: Hazard ratios for mortality by AD severity

Large ICER impact

Company assumes mortality risk is same in mild, moderate and severe AD

Figure: Annual mortality rate for company and EAG base case for AD health states



Does the committee consider that the company's approach to predicting mortality is suitable for decision making?

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

Key issue: Long-term treatment effect assumptions

Large ICER impact

Company and EAG disagree on modelled treatment effect duration and waning

Company

- Model simulation of 4 donanemab trials predicts that after treatment, amyloid plaques reaccumulate at a rate of 2.8 Centiloids (CL; 95% CI 2.2 to 3.1) per year
- Applying this assumption to amyloid PET imaging at Week 76 in TB-ALZ 2, indicates it would take ~3.5 years to return to amyloid positivity (>24.1 CL) after last treatment assuming linear increase over time – see appendix Biomarker results from TB-ALZ 2
- TB-ALZ 2 trial showed that in patients stopping donanemab early at 24 or 52 weeks due to amyloid clearance (positive stopping rule, then switched to placebo), AD progression by CDR-SB continued to be slowed vs placebo after treatment stopping up to Week 76
- So, company assumes full treatment effect lasts 3.5 years after stopping for fixed 18-month treatment duration (90% in model)
  - For treat-to-clear (10% in model), company assumes full treatment effect lasts 4 years after stopping at 12 months and 4.5 years after stopping at 6 months

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CL, centiloids; PET, positron emission tomography

Key issue: Long-term treatment effect assumptions

Large ICER impact

Company and EAG disagree on modelled treatment effect duration and waning

EAG comments

- Limited evidence about treatment effect beyond 18-month trial period
- Clinical experts: company's approach is speculative, lack of data
- EAG assumes 1-year full treatment effect after stopping, and waning for 2.5 years
  - In line with company's estimated 3.5 years return to amyloid positivity after stopping
- All patients have fixed 18-month treatment duration (0% treat-to-clear)

Table: Duration of treatment effect and waning

Assumption	Company base case	EAG base case
On treatment (trial): full effect	18 months	18 months
Off treatment: full effect	3.5 years	1 year
Off treatment: waning	5 years	2.5 years
= Total duration	10 years	5 years

- Applying EAG preferred assumptions to company base case increases ICER from £19,736 to £45,266

Question for clinical experts: Are the company's assumptions reasonable?

Abbreviations: ICER, incremental cost-effectiveness ratio

Key issue: Patient utility values

Small ICER impact

Company and EAG disagree on patient utility values

Company

- TB-ALZ 2 trial used QoL-AD measure: patient and proxy assessed HRQoL showed no significant difference between treatment arms
  - See appendix – QoL-AD results from TB-ALZ 2 trial
- Model uses caregiver-assessed patient utility values from Landeiro et al. 2020 fixed-effects meta-analysis for mild, moderate and severe AD
  - Pooled estimates of EQ-5D scores with different country-specific value sets

EAG comments

- Company approach not in line with NICE Reference case – values should be derived from representative sample of UK population
- Concerned about UK generalisability of company source
- EAG prefers to use GERAS study for EQ-5D scores from caregiver-assessed utility estimates for mild, moderate and severe AD

Abbreviations: EQ-5D, EuroQol-5 domains; HRQoL, health-related quality of life; QoL-AD, quality of life in Alzheimer's disease

Key issue: Patient utility values

Small ICER impact

Company and EAG disagree on patient utility values

EAG comments continued

- GERAS study conducted in UK, France and Germany, but UK value set used to derive utilities
- Explores scenario using GERAS UK subpopulation
- Uses general population utility for MCI value (as does company)
- Applying EAG preferred utilities to company base case increases ICER from £19,736 to £24,601

Table: Patient utilities

Health state	Company model (Landeiro et al)	EAG preferred (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

Does the committee consider that the company's patient utility values are suitable for decision making? What are the committee's preferred estimates for use in the model?

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

Key issue: Caregiver utility values

Large ICER impact

Company and EAG disagree on caregiver utility values

Company

- Considered EQ-5D not sensitive enough to measure HRQoL of caregivers for people with AD
- Conducted 2 vignette studies to derive caregiver utilities using time trade-off approach
  - Reported by general population participants
- Uses 1.8 caregivers per patient (GERAS study – UK subpopulation)

Table: Caregiver utilities used in Company model

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

EAG comments: Company approach for utilities not in line with NICE Reference case

Abbreviations: AD, Alzheimer's disease; EQ-5D, EuroQol-5 domains; HRQoL, health-related quality of life; MIC, mild cognitive impairment

Key issue: Caregiver utility values

Company and EAG disagree on caregiver utility values

Large ICER impact

EAG comments continued

- EAG prefers to base utility estimates on GERAS study, which reports EQ-5D for primary caregiver in Community. EAG models disutility for primary caregiver so uses 1 caregiver per patient as impact expected to be greater than on secondary caregiver
- Applying EAG preferred assumptions to company base case increases ICER from £19,736 to £37,722

Table: Caregiver utilities used by EAG and scenario

Health state	EAG preferred (GERAS adjusted)	EAG scenario (based on company's vignettes)	
	All	Spouse – Community	Child – Community All – Residential
MCI	0.81*	0.82	0.84
Mild AD	0.80*	0.79	0.74
Moderate AD	0.79	0.65	0.71
Severe AD	0.76	0.49	0.64

*General population utility used since GERAS value > gen. pop.

Does the committee consider that the company's carer utility values are suitable for decision making? What are the committee's preferred estimates for use in the model?

Abbreviations: AD, Alzheimer's disease; EQ-5D, EuroQol-5 domains; ICER, incremental cost-effectiveness ratio; MIC, mild cognitive impairment

Modelled costs: company, EAG and NHSE

Small or moderate ICER impact

Some differences in costs estimated by the company and EAG

EAG comments

- Company approach not in line with NICE Reference case – include unpaid care costs
- EAG adopted most of the company's costs in its base case but with some differences

Table: Differences in costs in company and EAG base cases

	Company base case	EAG base case	ICER impact
Healthcare resource use	Wittenberg et al., including unpaid care costs Applied terminal care costs	Used Wittenberg et al., but not including unpaid care costs Did not apply terminal care costs to avoid double counting	Moderate
Outpatient consultant visits	0 assumed At clarification, added option to include in model (£222 per visit)	1 at diagnosis + 1 per cycle during treatment (3 over 18 months)	Small

Is the committee satisfied with the costs included by the company for healthcare resource use? Should outpatient visits be included?

Abbreviations: ICER, incremental cost-effectiveness ratio

See appendix for a full comparison of Diagnostic testing and monitoring costs

Large ICER impact (NHSE costs)

Modelled costs: company, EAG and NHSE

Some differences in costs in the NHS England model, notably for administration

EAG comments continued

NHSE model costs:

- Alternative NHSE unit costs were included by EAG as a scenario rather than as EAG base case because they were not fully reported so could not be verified by EAG
  - Key difference was treatment administration cost (IV, Q4W)

Table: Administration cost assumed

	Company base case	NHS England model	EAG base case
Administration	£207 (21/22 costs, SB12Z)	£565 (WD02Z cost uplifted)	Same as Company (£207) • Scenarios for NHSE model (£565) and EAG adjustment of model (£600)

- NHSE model scenario increases company base case ICER from £19,736 to £29,030
- NHSE model scenario increases EAG base case ICER from £149,531 to £178,773

What are the committee's preferred estimates for costs: company, EAG or NHSE?

Abbreviations: ICER, incremental cost-effectiveness ratio NHSE, NHS England

Summary of company and EAG base case assumptions

Differences between company and EAG base cases

Assumption	Company base case	EAG base case
Donanemab treatment duration	90% treated for fixed 18 months 10% treated until amyloid clearance	100% treated for fixed 18 months
Risk of residential care	Spackman et al. 2012	GERAS study (UK)
Mortality risk for AD	x2.55 general population for patients with mild, moderate and severe AD	Increase with severity in mild to severe AD; based on Crowell et al. (age 80)
Long-term treatment effect	After fixed 18 months treatment: full effect retained for 3.5 years, then waning over 5 years After amyloid clearance: full effect retained for 4 or 4.5 years, waning over 5 years	After fixed 18 months treatment: full effect retained for 1 year, then waning over 2.5 years

 Abbreviations: AD, Alzheimer's disease

Summary of company and EAG base case assumptions

Differences between company and EAG base cases continued

Assumption	Company base case	EAG base case
Patient utility	Landeiro et al., EQ-5D using values sets from different countries combined	GERAS study, EQ-5D using UK value set
Caregiver utility (number)	2 vignette studies (1.8 caregivers)	GERAS study (1 caregiver)
Healthcare resource use	Wittenberg et al., + Terminal care costs	Wittenberg et al. excluding unpaid care
Outpatient consultations	0 for diagnosis, 0 for monitoring	1 for diagnosis, 1 per model cycle for first 18 months for monitoring

Abbreviations: AD, Alzheimer's disease; EQ-5D, EuroQol-5 domains

Cost-effectiveness results

NICE National Institute for Health and Care Excellence

Model results for life years (LYs) – undiscounted

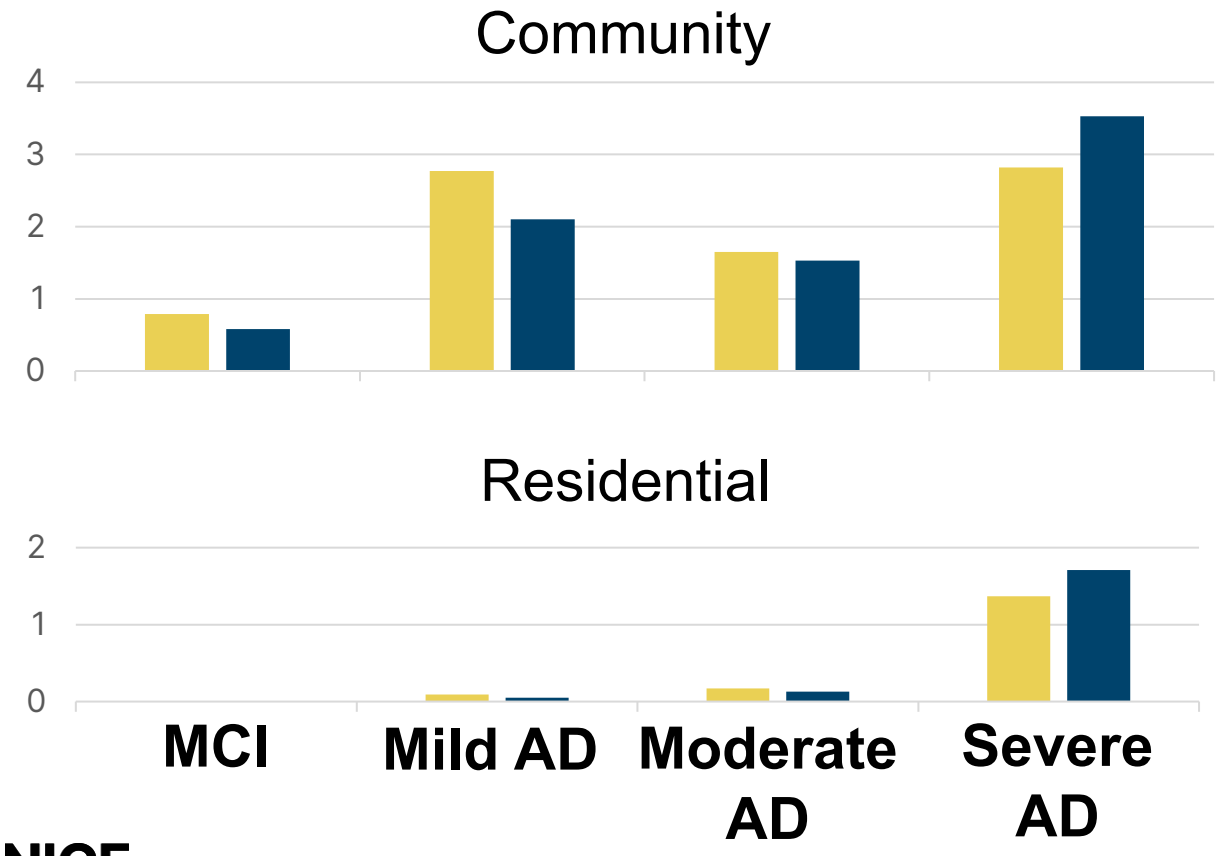
Some differences between company and EAG

Key: Donanemab BSC

Figures: Undiscounted patient LYs spent by health state

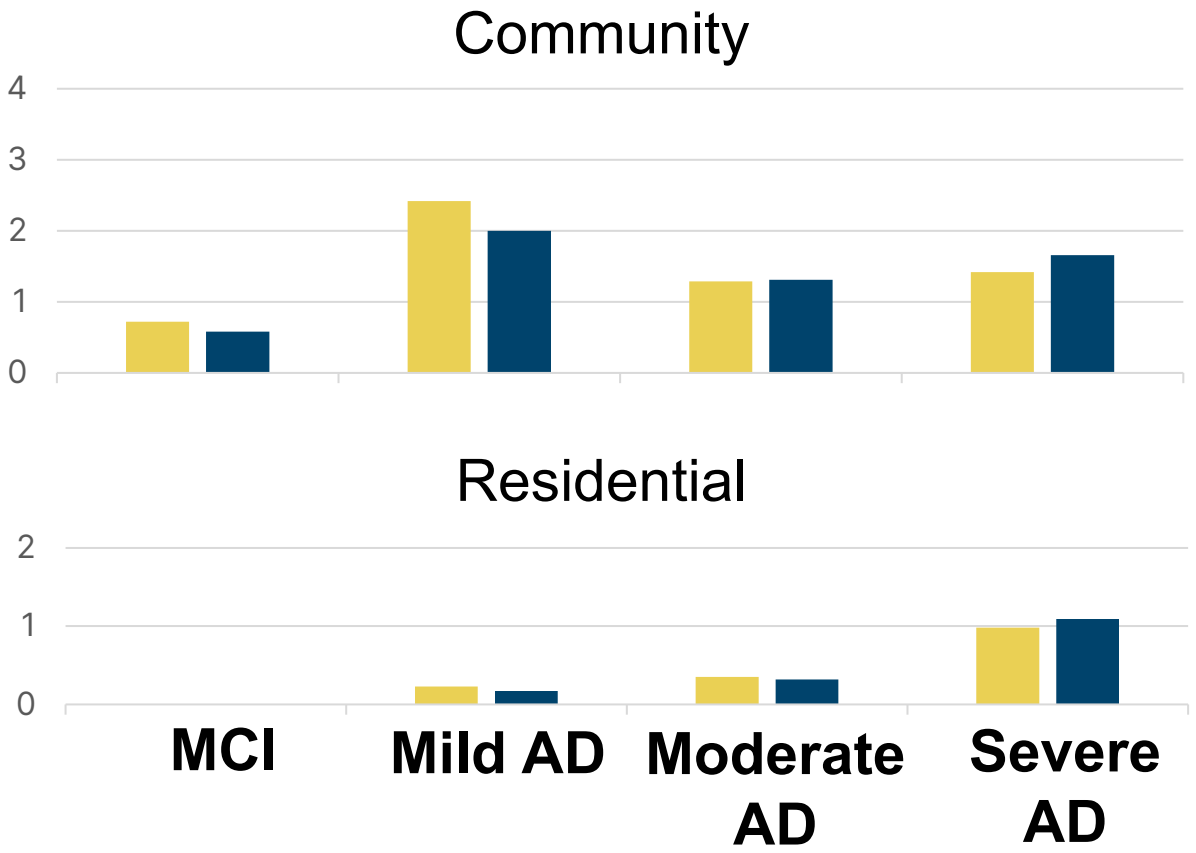
Company base case

- Total LYs: 9.7 donanemab, 9.6 BSC



EAG base case

- Total LYs: 7.4 donanemab, 7.1 BSC



Abbreviations: AD, Alzheimer's disease; BSC, best supportive care; LYs, life years; MCI, mild cognitive impairment

See appendix for Company scenarios

Cost-effectiveness results: company base case summary

Table: Company updated base case (deterministic, PAS price)

Technology	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	7.75	1.76	£13,953	0.02	0.71	£19,736
Best supportive care	[redacted]	7.73	1.05	-	-	-	-

Table: Company updated base case (probabilistic, PAS price)

Technology	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	1.83	£13,715	0.71	£19,395
Best supportive care	[redacted]	1.13	-	-	-

Note: The company base case was updated at the clarification stage (shown here), including a minor change in the model and an acknowledgement that the evaluation does not meet the criteria for a severity modifier

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

Cost-effectiveness results: EAG base case summary

Table: EAG base case (deterministic, PAS price)

Technology	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	6.27	3.89	£33,725	0.22	0.23	£149,531
Best supportive care	[redacted]	6.06	3.67	-	-	-	-

Table: EAG base case (probabilistic, PAS price)

Technology	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	6.35	3.83	£33,542	0.22	£151,133
Best supportive care	[redacted]	6.14	3.61	-	-	-

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

Cost-effectiveness results: EAG base case

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

Changes applied to company base case	Technology	Total costs (£)	Total QALYs	ICER (£/QALY)
Company updated base case	Donanemab	[redacted]	1.76	**£19,736**
	BSC	[redacted]	1.05	-
+ No patients discontinue due to reaching amyloid clearance before 18 months	Donanemab	[redacted]	1.76	£20,291
	BSC	[redacted]	1.05	-
+ Full treatment effect for 1 year after stopping, then 2.5 years waning	Donanemab	[redacted]	1.52	£46,113
	BSC	[redacted]	1.05	-
+ Annual probabilities of moving to residential care from the GERAS study	Donanemab	[redacted]	1.81	£51,314
	BSC	[redacted]	1.37	-
+ Mortality hazard ratios taken from Crowell 2023	Donanemab	[redacted]	1.95	£73,558
	BSC	[redacted]	1.53	-

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

Cost-effectiveness results: EAG base case

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

Changes applied to company base case	Technology	Total costs (£)	Total QALYs	ICER (£/QALY)
+ Patient utility from GERAS study	Donanemab	[redacted]	2.20	£86,350
	BSC	[redacted]	1.84	-
+ Caregiver disutility from GERAS study	Donanemab	[redacted]	3.77	£134,039
	BSC	[redacted]	3.54	-
+ One caregiver per patient	Donanemab	[redacted]	3.89	£137,775
	BSC	[redacted]	3.67	-
+ Health care resource use does not include unpaid care costs	Donanemab	[redacted]	3.89	£145,894
	BSC	[redacted]	3.67	-

NICE

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

Cost-effectiveness results: EAG base case

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

Changes (applied to company base case)	Technology	Total costs (£)	Total QALYs	ICER (£/QALY)
+ Double counting of terminal care costs removed	Donanemab	[redacted]	3.89	£146,133
	BSC	[redacted]	3.67	-
+ One outpatient consultation for diagnosis process and per model cycle up to 18 months	Donanemab	[redacted]	3.89	£149,531
	BSC	[redacted]	3.67	-
EAG base case	Donanemab	[redacted]	3.89	**£149,531**
	BSC	[redacted]	3.67	-

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

See appendix for Company, NHSE model

Cost-effectiveness results: EAG, NHSE model scenarios

Table: NHSE model costs and resources scenarios applied to EAG base case (deterministic, PAS price)

NHSE scenario (applied to EAG base case)	Technology	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
EAG base case	Donanemab	[redacted]	3.89	£33,725	0.23	£149,531
	BSC	[redacted]	3.67	-	-	
NHSE model	Donanemab†	[redacted]	3.89			£178,773
	BSC	[redacted]	3.67			
NHSE model (adjusted*)	Donanemab†	[redacted]	3.89			£185,875
	BSC	[redacted]	3.67			

*EAG used 20/21 administration cost code

†NHSE model assumes different costs and resource use for donanemab arm compared with EAG (or company) base case

NICE

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHSE, NHS England; PAS, patient access scheme; QALY, quality-adjusted life year

Cost-effectiveness results: EAG scenarios

Table: EAG scenarios applied to EAG base case (deterministic, PAS price)

Scenario: EAG preferred assumption	EAG scenario value used	ICER (£/QALY)
EAG base case	-	£149,531
Early discontinuation due to amyloid clearance: 0%	10%	£147,742
Transition probabilities: NACC (prevalent cohort, no improvement)	Potashman (prevalent, no improvement)	£143,059
	Potashman (prevalent, with improvement)	£135,885
Risk of residential care: GERAS study	Lin et al. 2022	£145,686
Mortality hazard ratios: Crowell et al. 2023	Ross et al. 2022	£162,803
	Lin et al. 2022	£153,570
*Company updated base case assumption	ONS 2023*	£213,392

Abbreviations: ADCER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre; PAS, patient access scheme; QALY, quality-adjusted life year

Cost-effectiveness results: EAG scenarios

Table: EAG scenarios applied to EAG base case (deterministic, PAS price)

Scenario: EAG preferred assumption	EAG scenario value used	ICER (£/QALY)
EAG base case	-	£149,531
Treatment effect of donanemab: Using CDR-SB	Using iADRS	£196,951
Long-term treatment effect after discontinuation due to AE: • Full effect for 1 year after stopping, then waned for 2.5 years	1 year waning	£155,702
Long-term treatment effect for discontinuation after fixed 18 months treatment or after amyloid clearance: • Full effect for 2.5 years (18 months + 1 year after stopping), then waned for 2.5 years *Company updated base case assumption	2.5 years full effect, 1 year waning	£184,546
	2.5 years full effect, 3 years waning	£141,905
	5 years full effect, 5 years waning*	£94,223

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Cost-effectiveness results: EAG scenarios

Table: EAG scenarios applied to EAG base case (deterministic, PAS price)

Scenario: EAG preferred assumption	EAG scenario value used	ICER (£/QALY)
EAG base case	-	£149,531
Patient utilities: GERAS study (overall population)	Landeiro study*	£117,053
	GERAS (UK)	£151,278
Caregiver utilities: GERAS study	Company vignettes*	£113,680
	Company vignettes (EAG adjusted)	£120,530
Mean number of caregivers per patient: 1	1.8*	£145,476

*Company updated base case assumption

See appendix for Impact of company scenarios

 Abbreviations: ICER, incremental cost-effectiveness ratio; 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 key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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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
- Availability of DMT could also have far-reaching implications and is likely to lead to the evolution of clinical care pathways in the NHS that will in turn, 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 APOE-4 homozygous

EAG: meta-analysis of trial outcomes

- Results for iADRS from TB-ALZ 2 trial and CDR-SB and iADRS from TB-ALZ and TB-ALZ 2 trials not included in modelling – requested the company provide meta-analysis of these so that impact of outcome measure could be further explored but this was not provided

Abbreviations: AD, Alzheimer's disease; APOE-4, apolipoprotein E 4; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; DMT, disease-modifying therapy; iADRS, Integrated Alzheimer's Disease Rating Scale

Aspects not captured in modelling

Uncaptured impact on patients, carers, and NHS services

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

Abbreviations: AD, Alzheimer's disease; IV, intravenous; MRI, magnetic resonance imaging; QALY, quality-adjusted life year

Company's managed access proposal

Uncertainties from the company:

- Limited duration of clinical trials so long-term benefits uncertain
- Lack of comprehensive cost data for care of people with AD in UK
- Due to lack of existing treatment for MCI, limited incentive to diagnose currently and uncertainty in demand for treatment

Proposed real world evidence sources:

- Long-term effectiveness studies in US and Europe (vs placebo)
- Planned study of resource use in UK for MCI due to AD and mild AD (results expected Q4 2024)
- Planned study of diagnosis and disease management in UK, including use of biomarkers (results expected 2024-2026)

Table: Company's TRAILBLAZER study plans

Study	Design
TB-ALZ EXT	Open label long-term extension (results expected [redacted])
TB-ALZ 2	Long-term extension (results expected Q4 2024)
TB-ALZ 3	In preclinical AD
TB-ALZ 4	Comparison with aducanumab in early symptomatic AD
TB-ALZ 5	Comparison with placebo in early symptomatic AD
TB-AZL 6	Impact of dosing on ARIA
TB-REAL OUS & TB-REAL US	Comparison with usual care alone, looking at dependence level in early symptomatic AD

Abbreviations: AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormality; MCI, mild cognitive impairment; Q4, quarter 4

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 • Extensive barriers to data collection in the NHS, e.g. need to ask both primary and secondary care to record assessment results • No NHS-level data collection is proposed, so the most feasible way to gather further data may be via the described trials rather than real-world data in clinical practice

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

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

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

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Key issues

	Issue (EAG report key issue number)	ICER impact
Clinical-effectiveness	Use of AChE inhibitors and memantine – see appendix (1)	Minimal
	Outcome measure used for treatment effect (2)	Moderate (scenario)
	Analysis of clinical effectiveness results (3)	Unknown
	Potential impact of risk of bias in trials (4)	Small (for base case)
	Impact of APOE-4 allele status (5)	Unknown
Cost-effectiveness	Hazard ratios for mortality by Alzheimer's disease severity (6)	**Large**
	Long term treatment effect assumptions (7)	**Large**
	Patient utility values (8)	Small
	Carer utility values (9)	**Large**
Others	Modelled costs: company, EAG and NHSE	**Large** (NHSE)

Abbreviations: AChE, acetylcholinesterase; APOE-4, apolipoprotein E 4; NHSE, NHS England

Key questions for the committee

	Key questions
Clinical-effectiveness	Is the donanemab trial data generalisable to the UK? Is the high use of concomitant medications expected to influence the trial results for donanemab?
	Are the outcomes measured (CDR-SB used in model) and the analysis of results suitable for decision making? Are other analyses needed: trial data, risk of bias?
	Are further analyses needed based on AOPE-4 mutation status?
Cost-effectiveness	Is the company's model appropriate for decision-making?
	What is the preferred approach for predicting mortality in the model?
	How should donanemab long-term treatment effect be modelled? How long should full treatment effect last after stopping? What is preferred for waning?
	Patient utility: what are the preferred estimates for use in the model?
	Caregiver utility: what are the preferred estimates? How many caregivers?
	Which costs and resource use should be included in the model?
Managed access	Is donanemab considered suitable for managed access?

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

Thank you

NICE National Institute for Health and Care Excellence

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Implementation challenges for donanemab

Identifying, assessing, testing, delivering, treating and monitoring patients

Implementation challenges identified by NHSE, patient and clinical experts, NICE System and National Implementation Teams, Medicines Optimisation Team:

- Increase in demand on primary care, memory clinics and other local services as awareness of MCI and DMT treatment options increases
- New neurology / psychiatry / geriatric medicine clinics being established will take time
- Increase in PET-CT and lumbar puncture capacity, neither of which are currently routinely used in the diagnosis of Alzheimer's
- Increase in MRI capacity
- New requirement for amyloid radiotracer supply

Abbreviations: DMT, disease-modifying treatment; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NHSE, NHS England

Implementation challenges for donanemab

Identifying, assessing, testing, delivering, treating and monitoring patients

Implementation challenges continued:

- Expansion of genetic testing (with a new standalone APOE-4 test requirement) and counselling services
- Increases in demand on secondary care services for infusion and the management of ARIA
- Diagnostic pathway redesign – adding a treatment option without clear guidance will be a barrier

Abbreviations: APOE-4, apolipoprotein E 4; ARIA, amyloid-related imaging abnormality

See main deck – Treatment pathway

Radiotracer use in PET imaging of amyloid

Licensed for diagnostic use. Company [redacted]

Company

- 3 amyloid-PET radiotracers approved in UK by MHRA (see Table)
- Specific radiotracer manufacturers included in license
- Indicated for 'PET imaging of β-amyloid neuritic plaque density in brains of adults with cognitive impairment being evaluated for AD and other causes of cognitive impairment'
- All indicated 'for diagnostic use only', for use 'in conjunction with clinical evaluation'

Table: Tracers used in diagnosing AD by PET

Radiotracer	License holder (Trade name)
Florbetapir	Eli Lilly (Amyvid)
Flutemetamol	GE Healthcare AS (VIZAMYL)
Florbetaben	Life Molecular Imaging GmbH (Neuraceq)

Florbetapir: [redacted]

- [redacted]

Abbreviations: AD, Alzheimer's disease; MHRA, Medicines and Healthcare products Regulatory Agency; PET, positron emission tomography; Q3, quarter 3

See main deck – Key clinical trials

TB-AZL 2: Baseline characteristics – overall population

Characteristic		Donanemab (n=860)	Placebo (n=876)
Age	Mean age, years (SD)	73.0 (6.2)	73.0 (6.2)
Sex	Female, n (%)	493 (57.3)	503 (57.4)
Race, n (%)	White	781 (90.9)	807 (92.1)
	Black or African American	19 (2.2)	21 (2.4)
	Asian	57 (6.6)	47 (5.4)
	American Indian or Alaska native	2 (0.2)	0
ApoE4 carrier status, n (%)	Non-carrier	255	250
	Heterozygous	452	474
	Homozygous	143	146
Use of AD symptomatic medication at baseline, n (%)	Yes	521 (60.6)	538 (61.4)

Abbreviations: AD, Alzheimer's disease; APOE-4, apolipoprotein E 4; n, number; SD, standard deviation

See main deck – Key clinical trials

TB-AZL 2: Baseline characteristics – overall population

Characteristic		Donanemab (n=860)	Placebo (n=876)
AD severity by MMSE at screening, n (%)	MCI due to AD	146 (17.0)	137 (15.7)
	Mild AD	713 (82.9)	738 (84.3)
	Moderate AD	1 (0.1)	0
AD severity by MMSE at baseline, n (%)	MCI due to AD	142 (16.7)	124 (14.3)
	Mild AD	514 (60.5)	526 (60.6)
	Moderate AD	194 (22.8)	218 (25.1)
CDR-G score, n (%)	0	2 (0.2)	4 (0.5)
	0.5	514 (60.8)	532 (61.2)
	1	304 (36.0)	308 (35.4)
	2	25 (3.0)	25 (2.9)
Amyloid biomarker	Plaque level, Centiloids	103.5 (34.5)	101.6 (34.5)

Abbreviations: AD, Alzheimer's disease; CDR-G, Global Clinical Dementia Rating; MCI, mild cognitive impairment; MMSE, mini-metal state examination; n, number; SD, standard deviation

Minimal ICER impact

Key issue: Use of AChE inhibitors and memantine

High use of concomitant AD medications in trials, including off-label in MCI

Company

- Use of concomitant symptomatic medications was stable through TB-ALZ 2 trial
  - Off-label use in people with MCI at screening: 45.2% used AChE inhibitors and 13.4% used memantine at screening*
- An Adelphi survey recently reported that [redacted] people with MCI used AChE inhibitors

EAG comments

- ~60% in TB-ALZ 2 and TB-ALZ used AChE inhibitors or memantine at baseline – use in trials is higher than expected in UK clinical practice (and outside NICE scope)
- Clinical experts agreed that some people with MCI have AChE inhibitors off-label – one thought [redacted] seemed realistic, another's experience was that <20% of people with MCI have AChE inhibitors
- Neither clinical expert said people with MCI received memantine in clinical practice

*Correction to company's clarification response

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

Key issue: Use of AChE inhibitors and memantine

Minimal ICER impact

High use of concomitant AD medications in trials, including off-label in MCI

EAG comments continued

Likely impact

- At clarification, company presented analysis showing that change from baseline iADRS and CDR-SB scores were not significantly different between people using key medicines at baseline and those not (see Table)
- Concomitant medication use not expected to impact on cost-effectiveness estimates (based on CDR-SB, used on model)

Table: Baseline medication use subgroup analysis of TB-ALZ 2 trial CDR-SB outcome at 18 months – evaluable efficacy set

Outcome	CDR-SB (NCS2 analysis)	
Baseline AChEI or memantine use	Yes	No
LS mean treatment difference at Wk 76 (95% CI) [p-value]	-0.71 (-1.02, -0.40) [<0.001]	-0.61 (-1.0, -0.23) [0.002]
P-value for interaction test	p≥0.317	

How much off-label use of AChE inhibitors or memantine is seen in clinical practice? Would use of these medicines impact the results of measures of cognition and function in people with MCI or mild dementia due to AD?

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, integrated Alzheimer's disease rating scale; LS, least squares; MCI, mild cognitive impairment; NCS2: natural cubic spline with 2 degrees of freedom; Wk, week

See main deck – Clinical trial results

Clinical trial results: key outcome measures

Descriptions of outcomes and what might be clinically meaningful change

iADRS is composite score with 2 domains:

- Cognitive ability (uses ADAS Cog13)
- Functional ability (uses ADCS ADL)

It assesses the impact of cognitive loss on the ability to conduct everyday activities as a single summary score of global AD severity. iADRS captures clinical progression and treatment effects from MCI due to AD through moderate dementia due to AD

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

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

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

Faculty of Public Health: Minimum clinically important CDR-SB difference is 0.98 in MCI and 1.63 in mild AD, but donanemab treatment effect is <half of that in mild AD

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADCS ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment

See main deck – Clinical trial results

Clinical trial results: key outcome measures

Descriptions of outcomes and what might be clinically meaningful change

Association of British Neurologists:

- No consensus and differing views whether benefits are clinically meaningful or meet minimal clinically important difference
- High uncertainty of effect on longer term trajectory of cognitive decline

Royal College of Psychiatrists:

- Trial: meaningful but modest clinical benefit
- 4-6 months "Time saved"
- Very limited data on long term benefits

UCL Dementia Research Centre:

- Slowing progression by >20% over 18 months or longer is clinically significant

Table: EAG summary [EAG report Table 10]

CDR-SB point change	MCI	Mild AD
Meaningful within-patient change (company)	1 point	2 points
Minimal clinically important difference (Andrews et al.)	0.98 point	1.63 points
Clinically meaningful change (Lansdall et al.), 'minimal' or 'moderate' deterioration	1 or 2.5 points	NR

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MIC, mild cognitive impairment; NR, not reported

See main deck – Analysis of clinical effectiveness results
See main deck – Potential impact of risk of bias in trials

Company's sensitivity analysis of key clinical outcomes by imputation method

Sensitivity analysis of TB-ALZ 2 results supported findings of key primary results

Company

- The primary efficacy analyses were based on modified ITT population (including participants with a baseline and at least one postbaseline efficacy measurement based on randomised treatment)
- At clarification, company provided sensitivity analyses for TB-ALZ 2 outcomes of CDR-SB and iADRS for the full ITT population with imputation of missing values to test robustness of primary efficacy analyses
- Sensitivity analysis of TB-ALZ2 results showed that donanemab slowed the progression of AD relative to people receiving placebo (see Table on next slide)

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale; ITT, intent-to-treat

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See main deck – Analysis of clinical effectiveness results
See main deck – Potential impact of risk of bias in trials

Company's sensitivity analysis of key clinical outcomes by imputation method

Sensitivity analysis of TB-ALZ 2 results supported findings of key primary results

Company

Table: Sensitivity analyses of TB-ALZ 2 efficacy results by imputation method

Analysis used for LS mean change difference between trial arms	CDR-SB (MMRM)		iADRS (NCS2)	
	Donanemab	Placebo	Donanemab	Placebo
TB-ALZ 2 trial: LS mean difference at Week 76 (95% CI) [p value]	-0.70 (-0.95, -0.45) [p<0.001]		2.92 (1.51 to 4.33) [p<0.001]	
• TB-ALZ 2 trial: With missing at random imputation	[redacted]		[redacted]	
• TB-ALZ 2 trial: With missing not at random imputation	[redacted]		[redacted]	
TB-ALZ trial: LS mean difference at Week 76 (95% CI) [p value]	-0.36 (-0.83, 0.12) [p=0.139]		3.20 (0.12, 6.27) [p=0.04]	

Abbreviations: CI, confidence interval; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale; LS, least squares; MMRM, mixed models for repeated methods; NCS2, natural cubic spline with 2 degrees of freedom

See main deck – Potential impact of risk of bias in trials

Company's sensitivity analysis of key clinical outcomes with censoring for first ARIA and infusion-related reactions

Sensitivity analysis of TB-ALZ 2 results in line with findings of key primary results

Company

Table: TB-ALZ 2 HR for progression with censoring for first ARIA and IRR

Analysis used	HR for progression for donanemab vs placebo (95% CI)	
	CDR-SB	iADRS
Original analysis	0.623 (0.519 to 0.748)	0.70 (0.582 to 0.842)
• Censored ARIA and IRR	[redacted]	[redacted]

- Patients were censored at their first occurrence of ARIA or IRR if they had not already experienced disease progression. Note that participants who experienced an ARIA event or IRR after the 1st visit, where a clinical worsening occurred, but before the 2nd consecutive visit were considered as having had an event and were not censored
- Number of events (due to censoring) drops more in donanemab arm than placebo arm
- Impact of additional censorings is limited because they occur early in treatment period
- Not expected to meaningfully change economic model results (impacts not provided)

Abbreviations: ARIA, amyloid related imaging abnormality; CI, confidence interval; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; HR, hazard ratio; iADRS, integrated Alzheimer's Disease Rating Scale; IRR, infusion related reaction

See main deck – Long-term treatment effect assumptions

Biomarker results from TRAILBLAZER-ALZ 2

Donanemab reduces brain amyloid over 18 months

Company results:

- Baseline amyloid plaque level was similar in the 2 treatment arms: ~100 Centiloids
- 76% of people treated with donanemab had amyloid clearance by Week 76 (Table)

Figure: Amyloid PET adjusted mean change

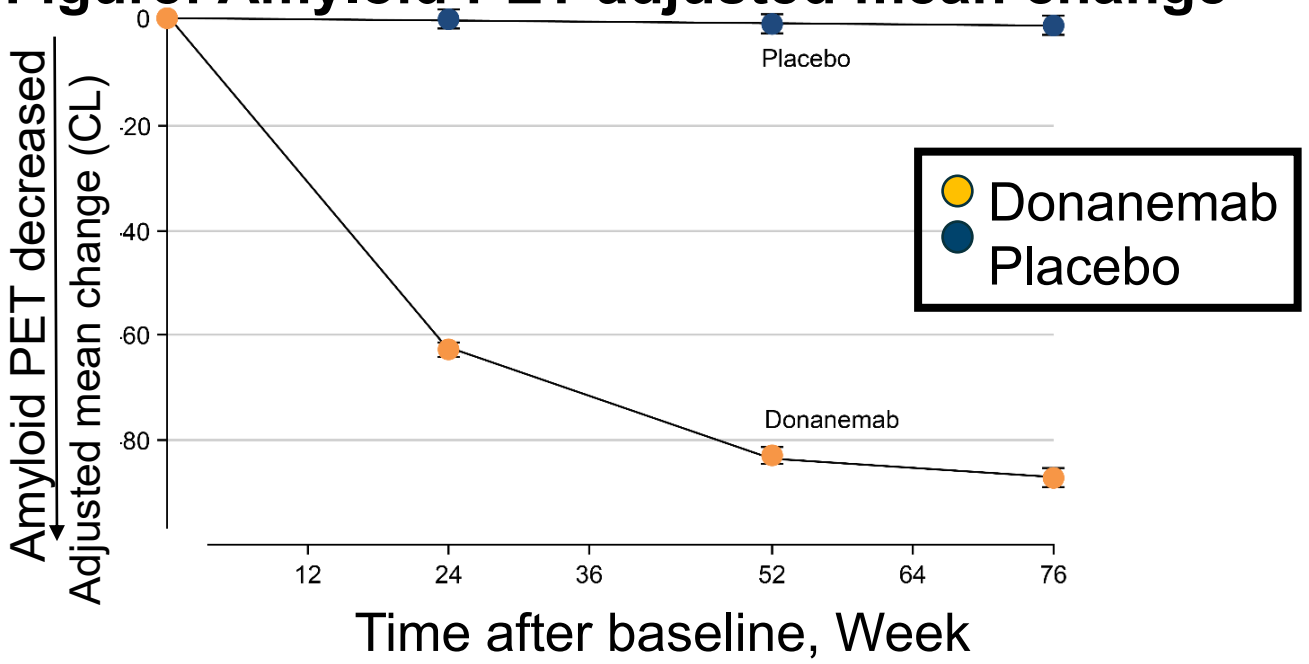

Table: TB-ALZ 2 trial amyloid biomarker outcome at 18 months

Outcome	Donanemab	Placebo
N at Baseline, Week 76	765, 614	812, 690
Adj. mean change at Wk 76, CL (95% CI)	-87.0 (-88.90, -85.17)	-0.67 (-2.45, 1.11)
Amyloid clearance to <24.1 CL at Wk 76, % (95% CI)	76.4% (72.87%, 79.57%)	0.3% (0.08%, 1.05%)

Abbreviations: Adj., adjusted; CI, confidence interval; Cl, centiloids; N, number

See main deck – Patient utilities

HRQoL results from TRAILBLAZER-ALZ 2

No statistically significant change in AD-specific HRQoL measure

Company approach to measuring HRQoL in TB-ALZ 2:

- Company: EQ-5D has some limitations in reflecting full impact of AD progression on patients' QoL so it was not used in trial. Also, caregivers' own QoL not assessed in trial
- In TB-ALZ 2: Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire was used in a subset of patients, a 13-item disease-specific questionnaire
  - Rates on a scale of 1–4 (poor, fair, good, or excellent) life domains including physical health, mood, relationships, activities, and ability to complete tasks
    - QoL worsening = decrease in score (negative change)
- **Results:** no significant difference between treatment arms in HRQoL (see Table)

Table: TB-ALZ 2 trial HRQoL outcome at 18 months

QoL-AD result	Patient-assessed		Proxy-assessed	
	Donanemab	Placebo	Donanemab	Placebo
N	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change in score from Baseline to Wk 76	[redacted]	[redacted]	[redacted]	[redacted]
LS mean treatment difference at Wk 76 (95% CI) [p-value]	[redacted]		[redacted]	

EAG: QoL-AD a valid and reliable measure

Abbreviations: see slide notes

See main deck – Company's model overview

How the technology affects costs and QALYs

Summary of model drivers

- Technology affects **costs** by:
  - Increased acquisition costs
  - Increased administration costs
  - Increased monitoring costs

- Technology affects **QALYs** by:
  - Increasing time spent in MCI or mild AD health state
  - Slowing disease progression

- Assumptions with greatest ICER effect:
  - Duration of treatment effect
  - Mortality hazard ratios
  - Caregiver disutilities
  - Costs and resource use

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

See main deck – Company's model: risk of residential care

Company's model: transition probabilities

Company's transition probabilities accepted

- Company used US NACC dataset for the CDR-SB-defined health states:

Table: Annual health state transition probabilities

Health state transition	Company model
MCI to Mild AD	26.6%
MCI to Moderate AD	1.4%
MCI to Severe AD	0.2%
Mild AD to Moderate AD	30.5%
Mild AD to Severe AD	3.0%
Moderate AD to Severe AD	36.0%

EAG comments

- Agreed with company's approach

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

See main deck – Key issue: Hazard ratios for mortality by AD severity

Company's hazard ratios for mortality

Company provided option for variable mortality risk at clarification

Company

- At clarification company provided option to vary mortality HR by AD severity for mild, moderate and severe AD (US NACC dataset) as a scenario

Table: Mortality risk for AD compared with general population

Health state	Company base case (ONS)	Company explored (NACC)	EAG base case (Crowell et al)
MCI	1	1	1
Mild AD	2.55	1.79*	2.4
Moderate AD	2.55	1.75*	3.1
Severe AD	2.55	3.41	6.6

*Confidence intervals of HR point estimates overlap

- Company's variable mortality scenario increased company base case ICER from £19,736 to £29,819

Abbreviations: AD, Alzheimer's disease; HR hazard ratio; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre

See main deck – Modelled costs

Model inputs: Diagnostic testing and monitoring costs

Discrepancies in costs estimated by the company and NHS England

Table: Differences in relevant costs in company and NHSE models

Cost/resource use	Company base case	NHS England model	EAG base case
Administration	• £207 (21/22 costs, SB12Z) IV given Q4W	• £565 WD02Z cost uplifted IV given Q4W	Same as Company • Scenarios for NHSE model
MRI scans	• £197 (21/22, RD01A) 1x diagnostic in 75% patients 3x monitoring in 100% on treatment	• £191 (RZ02Z) 1x diagnostic in 100% patients 3x monitoring in 100% on treatment	Same as Company • Scenario for NHSE model
Amyloid PET-CT	Total: [redacted] • Scan: £607 (21/22, RN01A) • Tracer: [redacted] (assumed*) 10% patients (vs CSF)	Total: £1,000 (estimated) • Scan: £800 • Tracer £200 15% patients (vs CSF)	Same as Company • Scenario for NHSE model

*Draft price for amyloid tracer in UK ([redacted])

Abbreviations: CSF, cerebrospinal fluid; IV, intravenous; MRI, magnetic resonance imaging; NHSE, NHS England; PET-CT, positron emission tomography-computed tomography; Q4W, every 4 weeks

See main deck – Modelled costs

Model inputs: Diagnostic testing and monitoring costs

Discrepancies in costs estimated by the company and NHS England

Table: Differences in relevant costs in company and NHSE models

Cost/resource use	Company base case	NHS England model	EAG base case
CSF	• £406 (21/22, HC72A) • 90% patients (vs PET)	• £580 (HC72A) • 85% patients (vs PET)	Same as Company • Scenario for NHSE model
Blood biomarker	• £43 (21/22, DAPS02)	• Same as company	Same as company
APOE-4 testing	100% patients have: • Test: £44 (21/22, DAP02) 0% have outpatient appointment or counselling	100% patients have: • Test: £250 • Outpatient: £200 50% have counselling: £350 (WH16B)	100% patients have: • Test: £44 • Outpatient: £222 0% separate counselling visit

Abbreviations: APOE-4, apolipoprotein E4; CSF, cerebrospinal fluid; IV, intravenous; MRI, magnetic resonance imaging; NHSE, NHS England; PET, positron emission

Cost-effectiveness results: company scenarios

See main deck – Company base case

Table: Company scenario analyses (deterministic, PAS price)

No.	Scenario (applied to company base case)	ICER (£/QALY)
Company updated base case		£19,736
1	Discount rate of 1.5%	£15,855
2	100% patients enter model in MCI due to AD	£7,783
3	100% patients enter model in mild dementia due to AD	£23,878
4	Fixed duration of treatment only	£20,291
5	Treat-to-clear only	£14,209
6	4 diagnostic tests required to identify 1 eligible patient	£21,283
7	Blood-based biomarker test becomes available (rule-out)	£19,024
8	Blood-based biomarker test becomes available (rule-in)	£18,251
9	Transition probabilities (Potashman et al.)	£19,069
10	Caregiver utility values (unadjusted)	£22,654

NICE

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

Cost-effectiveness results: company scenarios

See main deck – Company base case

Table: Company scenario analyses (deterministic, PAS price)

No.	Scenario (applied to company base case)	ICER (£/QALY)
Company updated base case		£19,736
11	Treatment effect waning (medium-term) based on amyloid positivity level of 30cL	£18,068
12	Patients who discontinue due to AE wane treatment over 10 cycles	£18,389
13	Patients who discontinue due to AE wane treatment over 1 cycle	£21,302
14	Treatment waning effect applied over 5 cycles (patients who did not discontinue due to AE)	£23,239
15	Treatment waning effect applied over 15 cycles (patients who did not discontinue due to AE)	£17,748
16	Mortality based on meta-analysis	£26,329
17	Direct Health and Social Care Costs (Wittenberg et al.)	£31,379
18	Informal care costs included (Wittenberg et al.)	£29,812

NICE

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

See main deck – EAG base case

Cost-effectiveness results: EAG, company scenarios

Table: Company scenarios applied to EAG base case (deterministic, PAS price)

Scenario: EAG preferred assumption	Company scenario value used	ICER (£/QALY)
EAG base case	-	£149,531
Discount rate: 3.5%	1.5%	£135,280
Initial patient population severity distribution: 20% MCI due to AD, 80% mild AD	100% MCI due to AD	£101,990
	100% mild AD	£166,905
Patients screened for amyloid clearance: 0%	100%	£129,959
Diagnostic tests required per eligible patient identified: 2	4	£154,381
Transition probabilities: NACC (prevalent, no improvement)	Potashman (incident, no improvement)	£143,492

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

See main deck – EAG base case

Cost-effectiveness results: EAG, company scenarios

Table: Company scenarios applied to EAG base case (deterministic, PAS price)

Scenario: EAG preferred assumption	Company scenario value used	ICER (£/QALY)
EAG base case	-	£149,531
Waning duration after discontinuation due to AE: 5 cycles	10 cycles	£142,466
	1 cycle	£158,172
Waning duration for discontinuation after fixed 18 months treatment duration or after amyloid clearance: 5 cycles	15 cycles	£108,566

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

See main deck – EAG, NHSE model

Cost-effectiveness results: NHSE model applied to company base case

Table: NHSE model costs and resources applied to company base case (deterministic, PAS price)

NHSE scenario (applied to company base case)	Technology	Total costs (£)	Total QALYs	ICER (£/QALY)
Company base case	Donanemab	[redacted]	1.76	£19,736
	BSC	[redacted]	1.05	
NHSE model	Donanemab†	[redacted]	1.76	£29,030
	BSC	[redacted]	1.05	
NHSE model (adjusted*)	Donanemab†	[redacted]	1.76	£31,252
	BSC	[redacted]	1.05	

*Using EAG's 20/21 administration cost code

†NHSE model assumes different costs and resource use for donanemab arm compared with company base case

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHSE, NHS England; PAS, patient access scheme; QALY, quality-adjusted life year

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

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])

Abbreviations: DSU, decision support unit; QALY, quality-adjusted life year