NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using donanemab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2025

Note that this document is not NICE's final guidance on donanemab. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using donanemab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 27 March 2025
- Third evaluation committee meeting: 14 May 2025.
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Donanemab is not recommended, within its marketing authorisation, for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease in adults who are apolipoprotein E4 heterozygotes or non-carriers.

1.2 This recommendation is not intended to affect treatment with donanemab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for mild cognitive impairment caused by Alzheimer's disease is best supportive care, and for mild dementia caused by Alzheimer's disease includes an acetylcholinesterase inhibitor (donepezil hydrochloride, galantamine or rivastigmine). Donanemab could be used at the same time as current treatments at these stages of Alzheimer's disease.

Evidence from clinical trials suggests that people having donanemab continue to have worsening cognitive function over time, but at a slower rate than people on placebo (both added to current treatment). There is a lack of evidence on the long-term effects.

There are substantial uncertainties in the economic model, including:

- the treatment-effect estimates
- what proportion of people starting donanemab would have mild cognitive impairment or mild dementia caused by Alzheimer's disease
- the risk of death associated with Alzheimer's disease
- how long the effects of donanemab last after stopping treatment

- the health-related quality of life of people with mild cognitive impairment or mild dementia caused by Alzheimer's disease, and their carers
- the infusion costs for donanemab.

The cost-effectiveness estimates for donanemab are also uncertain, but they are much higher than what NICE considers an acceptable use of NHS resources. Donanemab is not good value for the NHS because the benefit it provides for people with Alzheimer's disease is relatively small but the cost is high for providing it (including monthly infusions in hospital and intensive monitoring for side effects). So, donanemab is not recommended for routine use.

Because donanemab is unlikely to be cost effective and the uncertainties would not be fully addressed in a period of managed access, it is not recommended with managed access.

2 Information about donanemab

Marketing authorisation indication

2.1 Donanemab (Kisunla, Eli Lilly and Company) is indicated 'for the treatment of 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for donanemab.

Price

2.3 The list price of donanemab concentrate for solution for infusion is confidential until published by the Department for Health and Social Care.

2.4 The company has a commercial arrangement, which would have applied if donanemab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Eli Lilly and Company, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence. The first committee meeting was held before the full detail of the marketing authorisation for donanemab was available from the Medicines and Healthcare products Regulatory Agency. The committee discussion was based on the full population in the TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ trials, but also considered subgroups effects based on apolipoprotein (APO) E4 carrier status. At the second committee meeting, the committee discussion was based on the population indicated in the marketing authorisation (see section 3.4).

The condition

Alzheimer's disease

3.1 Alzheimer's disease is a progressive neurological condition, and the most common type of dementia. It affects 6 in 10 people with dementia, which is the leading cause of death in the UK. Alzheimer's disease is thought to be caused by the abnormal build-up of proteins in and around brain cells. One of these proteins is called amyloid beta. Deposits of amyloid proteins form plaques around brain cells and disrupt brain cell function. The largest risk factor for dementia is age. More than 95% of people affected are over 65 years. The APOE4 gene has also been associated with an increased risk of developing Alzheimer's disease. The patient experts explained that Alzheimer's disease affects people in different ways and advised against making general assumptions for all people with the condition. Statements from people living with Alzheimer's disease described the loss of independence and confidence when they had their diagnosis, and the hope that potential disease-modifying treatments would bring. The patient experts explained the significant role of carers in looking after people with Alzheimer's disease, and the life-changing effects of the condition on them. They noted that carers' emotional, financial and physical health are all affected by looking after someone with Alzheimer's disease.

Statements from carers described the stress and 'desperation' associated with becoming a full-time carer. The clinical experts explained that Alzheimer's disease is progressive, complex and not fully understood. They advised that the underlying pathology starts at least 10 years before symptoms present. The committee noted the first-hand experiences provided by people with Alzheimer's disease. It concluded that the condition is progressive, debilitating and affects people in different but significant ways. It also noted the substantial burden on the families and carers of people with the condition.

Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease

3.2 NICE's guideline on assessment, management and support for people living with dementia and their carers (NG97) makes recommendations for diagnosing Alzheimer's disease in the NHS. But the clinical and patient experts explained that NICE's guidelines are not always followed in clinical practice. This is because of challenges in accessing the recommended diagnostics and specialist services in some areas. Also, NICE's guideline does not include mild cognitive impairment caused by Alzheimer's disease, which refers to the set of symptoms that occur before the dementia stage of the condition. Patient and clinical experts noted that the different terms used to describe the stages of Alzheimer's disease, including from before having symptoms, can be confusing. Guidelines from the National Institute on Aging and the Alzheimer's Association define the mild cognitive impairment stage as mild changes in memory and thinking that:

- are noticeable and measurable
- do not disrupt a person's day-to-day life.

Mild dementia caused by Alzheimer's disease is defined as impairments in memory, thinking and behaviours that decrease a person's ability to function in day-to-day life. Alzheimer's disease usually develops slowly

from initial symptoms. Progression is characterised by deterioration in cognition and functional ability and associated behavioural and psychiatric symptoms. If the diagnosis is uncertain and Alzheimer's disease is suspected, NG97 recommends considering a positron emission tomography (PET) scan or cerebrospinal fluid test to check for presence of amyloid beta in someone with symptoms. The number of people diagnosed with mild dementia because of Alzheimer's disease in England is about 80,000. But more than a third of people with all types of dementia in England do not have a dementia diagnosis. The exact number of people with mild cognitive impairment caused by Alzheimer's disease is unknown. But it is estimated to be present in about 5% of people over 65 years and about 25% of people over 80 years. The clinical experts' opinion was that people with mild cognitive impairment caused by Alzheimer's disease will eventually progress to having dementia. In response to the draft guidance, the Faculty of Public Health noted there is no consensus that having amyloid positivity will always lead to Alzheimer's disease. Clinical experts also noted that most people do not have a confirmed diagnosis of mild cognitive impairment and there are no standardised measures to clearly separate the disease stages. They explained that some people diagnosed with mild cognitive impairment caused by Alzheimer's disease are followed up in secondary care. But many people are discharged from memory clinics back to primary care, with the advice to be re-referred once their symptoms progress. The committee noted there are challenges with the diagnosis of mild cognitive impairment and mild dementia caused by Alzheimer's disease in NHS clinical practice. But it recognised that diagnostic guidelines were not within its remit.

Clinical management

Treatment options

3.3 There are currently no pharmacological treatments for mild cognitive impairment caused by Alzheimer's disease. For mild, moderate or severe

dementia caused by Alzheimer's disease, NICE's guideline on dementia and NICE's technology appraisal guidance on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease recommend as options:

- the acetylcholinesterase inhibitors donepezil hydrochloride, galantamine and rivastigmine, all alone, for mild to moderate disease
- memantine alone:
  - for moderate Alzheimer's disease, only when acetylcholinesterase inhibitors are not tolerated or contraindicated
  - for severe Alzheimer's disease.

For people with an established diagnosis of Alzheimer's disease already on an acetylcholinesterase inhibitor, the recommended options are:

- adding memantine for moderate disease
- adding memantine for severe disease.

The clinical experts explained that current treatments for Alzheimer's disease have symptomatic benefits for some people, but none are disease-modifying. The committee acknowledged that current treatment options are very limited for mild dementia caused by Alzheimer's disease. It concluded that there is a significant unmet need for treatment options to slow or prevent progression from mild cognitive impairment or mild dementia caused by Alzheimer's disease to more severe stages.

Treatment positioning of donanemab

3.4 The company positioned donanemab based on the population identified in the marketing authorisation indication (see section 2.1), but narrowed it to exclude people with an unknown APOE4 status or having anticoagulants that are contraindicated. The company noted that this would be the population eligible in NHS practice. People with mild cognitive impairment caused by Alzheimer's disease or mild dementia caused by Alzheimer's disease with confirmed amyloid pathology could have donanemab

alongside established clinical management, including existing medicines. The clinical experts advised that because the treatment window for having donanemab is earlier and more limited than existing options that are for mild, moderate or severe dementia caused by Alzheimer's disease, timely diagnosis of Alzheimer's disease is much more important. The patient, clinical and commissioning experts explained that using donanemab (and other potentially disease-modifying treatments) in the NHS would require significant changes to the existing diagnostic pathway (see section 3.2). An outline of the new diagnostic pathway is shown in the committee papers in the submission from NHS England. The recommendations include:

- establishing specialist diagnostic clinics
- confirmatory diagnostic tests for amyloid beta pathology in cerebral spinal fluid (lumbar puncture) or with a PET-CT scan
- need for genetic testing for APOE4 (to exclude people who are APOE4 homozygotes).

NHS England advised that introducing disease-modifying treatments would substantially increase demand on primary care and memory clinics because of increased awareness of mild cognitive impairment and availability of treatment options. The committee noted that a blood test for amyloid beta is being developed but is not currently used in the UK. Commissioning experts advised that the treatment pathway for donanemab would be more complex than for current treatments, and would include:

- 4-weekly intravenous infusions of donanemab, started in secondary care
- routine outpatient follow-up appointments every 3 months
- routine MRIs during treatment
- acute management of amyloid-related imaging abnormalities (ARIA), including additional MRIs if needed.

The committee noted at the second meeting that the marketing authorisation for donanemab (see section 2.2) requires treatment is stopped on progression to moderate dementia caused by Alzheimer's disease. The committee concluded that donanemab (if recommended) would need a significant change to current diagnostic and treatment pathways in Alzheimer's disease.

Clinical effectiveness

Clinical trials

3.5 The main source of clinical-effectiveness evidence presented for donanemab was the TRAILBLAZER-ALZ 2 trial. This was a phase 3, randomised placebo-controlled double-blind trial. It investigated the efficacy of donanemab compared with placebo in people aged 60 to 85 years with early symptomatic Alzheimer's disease (mild cognitive impairment or mild dementia). The primary outcome of TRAILBLAZER-ALZ 2 was change in the integrated Alzheimer Disease Rating Scale (iADRS) at 76 weeks from baseline. People in the study had evidence of abnormalities in amyloid and tau proteins in the brain, by PET scan. TRAILBLAZER-ALZ 2 was done in 277 sites in 8 countries including the UK. The trial randomised 1,736 people (860 to donanemab and 876 to placebo). Overall, 76% of patients completed the 76-week study. The mean age was 73 years and 57% were women. The company presented clinical evidence from TRAILBLAZER-ALZ 2 for the overall population as the basis for decision making. In response to the draft guidance, the Faculty of Public Health commented that the trial population is not generalisable to the UK. It noted the difference in average age from TRAILBLAZER-ALZ 2 (73 years) and recent UK real-world data from the Cognitive Function and Ageing Study II (83 years). Clinical experts noted that the age of patients impacts factors including life expectancy, how aggressive progression of Alzheimer's disease is and likelihood of having the caregiver support that was expected to be needed for having treatment. The EAG noted that the company's phase 2 trial,

TRAILBLAZER-ALZ, had a similar design to TRAILBLAZER-ALZ 2. But the company did not include the phase 2 trial in its analysis of clinical effectiveness to inform the cost-effectiveness model. TRAILBLAZER-ALZ was done in 56 sites in the US and Canada. The mean age of people in the trial was 75 years and 52% were women. At clarification, the EAG asked the company to provide a meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ results to inform the clinical-effectiveness evidence. But the company did not provide this. The company explained that TRAILBLAZER-ALZ was a smaller study of donanemab compared with placebo (n=257). So, the results of a meta-analysis would be driven by TRAILBLAZER-ALZ 2. The company stated that differences between the 2 trials limited the feasibility and validity of a meta-analysis because their design and populations were not aligned. These differences included eligibility based on tau protein level, because people with a high brain tau level were excluded from TRAILBLAZER-ALZ. The EAG noted that the company does not anticipate the need to identify people with tau pathology when starting donanemab because it is a treatment that targets brain amyloid not tau. The EAG's clinical experts advised that the differences between the design of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ were unlikely to affect key outcomes or prevent a meta-analysis. The committee concluded at the first meeting that the results of both trials are relevant to the decision problem and should be explored by the company in a meta-analysis. At the second committee meeting, the company presented clinical-effectiveness results for the UK eligible population as the basis for decision making. This excluded from the overall trial population people who were homozygous for the APOE4 gene or had missing APOE4 status, and people having anticoagulants. The EAG noted that the company did not state how many trial participants contribute data to the analyses of the iADRS and the secondary outcome, clinical dementia rating scale sum of boxes (CDR-SB). The company presented its updated results for TRAILBLAZER-ALZ 2 and for a meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. The EAG

noted that the analysis combining data from TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ seemed to be pooled results of these trials rather than a meta-analysis using weighted pooled estimates. It noted that no random effects model to assess heterogeneity between the 2 trials had been presented. The committee decided that results for the UK eligible population for donanemab are suitable for use in decision-making. It also concluded that the pooled analyses of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ are relevant to the decision problem.

Clinical-effectiveness results

3.6 At the first meeting, the committee considered the results of the primary and a key secondary outcome in the trials. It noted that a decline in iADRS and CDR-SB score was seen in both arms but there was less of a decline with donanemab than with placebo. The main analysis method the company used to calculate change from baseline to week 76 for iADRS was a natural cubic spline with 2 degrees of freedom model and for CDR-SB was a mixed model for repeated measures. The results of these analyses are shown in table 1.

Table 1 Treatment difference at 76 weeks for donanemab compared with placebo on iADRS and CDR-SB in the modified intention-to-treat population

	iADRS		CDR-SB	
Trial (phase)	**Least squares mean difference (95% confidence interval) [p-value]**	**% difference**	**Least squares mean difference (95% confidence interval) [p-value]**	**% difference**
TRAILBLAZER-ALZ 2 (phase 3)	2.92 (1.51 to 4.33) [p<0.001]	22%	-0.70 (-0.95 to -0.45) [p<0.001]	29%
TRAILBLAZER-ALZ (phase 2)	3.20 (0.12 to 6.27) [p=0.04]	32%	-0.36 (-0.83 to 0.12) [p=0.139]	23%

The EAG noted that the treatment differences varied when comparing the results of the 2 key trials. The treatment difference was smaller for iADRS

and larger for CDR-SB in TRAILBLAZER-ALZ 2 compared with TRAILBLAZER-ALZ. The EAG advised that the reasons for this variability were not clear. It noted that the company did sensitivity analyses to explore the clinical-effectiveness results (see section 3.9). At the second committee meeting, the company presented its analyses of iADRS and CDR-SB results for the UK eligible population of TRAILBLAZER-ALZ 2 and for a pooled analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. These results cannot be reported because the company considers them to be confidential. The EAG stated that the results of the new analyses were consistent with the results of the company's original analysis. At the first committee meeting, the company presented results for subgroups based on the APOE4 allele status of trial participants. At the second committee meeting, the committee did not consider the results for homozygotes because this group was excluded from the marketing authorisation. The committee noted the company's statistical interaction test showed that the number of APOE4 alleles was not a treatment-effect modifier in the UK eligible population for donanemab. The committee decided that donanemab has a similar treatment effect in people who are heterozygous for the APOE4 allele or are non-carriers. The committee concluded that in the trials donanemab led to less of a decline in cognition and function scores than placebo at 76 weeks in the original and the updated UK eligible population.

Clinically meaningful treatment effect

3.7 The submission from the Association of British Neurologists stated it was unclear if the donanemab trial results were clinically meaningful and this is currently being debated in the clinical community. The Faculty of Public Health submission explained that literature suggests a minimum clinically important CDR-SB difference is 0.98 for mild cognitive impairment caused by Alzheimer's disease and 1.63 for mild dementia caused by Alzheimer's disease. The treatment effect seen with donanemab in TRAILBLAZER-ALZ 2 at 18 months was smaller than both of these values and may be about half of that considered clinically meaningful. The Royal College of

Psychiatrists stated that the observed treatment effect of donanemab in TRAILBLAZER-ALZ 2 was modest but clinically meaningful. The company and University College London Dementia Research Centre suggested that slowing disease progression by more than 20% over 18 months is clinically significant. In response to the draft guidance, the College of Mental Health Pharmacy stated that the change of less than 3 points in iADRS in TRAILBLAZER-ALZ 2 is less than it considered meaningful in mild cognitive impairment or mild dementia caused by Alzheimer's disease. At the first committee meeting, the EAG advised that European consensus is that slowing of progression by 30 to 50% is clinically meaningful. At the second committee meeting, the NHS commissioning expert suggested that clinical experts have highly differing views about the amount of change that is considered clinically meaningful. They noted that before the type of trial under consideration a larger change in CDR-SB was considered meaningful than was observed for donanemab. The clinical experts agreed with the company that slowing disease progression by more than 20% in the early stages of Alzheimer's disease, particularly in mild cognitive impairment, is an outcome that matters to patients and carers. This slowing of progression could maintain patients in their current state, and when there are no other disease-modifying treatment options this is meaningful. The committee noted at the first meeting that the company's primary analyses were of mean change from baseline data at week 76. These captured treatment difference at a single point in time (the end of the trial). It noted the company had also done time-based analyses. These looked at time taken to progress to a subsequent disease stage. The committee noted it was unclear what the threshold for progression was in the time-based analyses. It thought that time-based analyses may be more appropriate to show 'slowing' of disease progression than mean change from baseline. The committee concluded that donanemab had a clinically meaningful treatment effect. But, it noted that the treatment effect was small.

Measures of cognition and function

3.8 The committee considered the outcome measures presented for the clinical-effectiveness results. iADRS is a composite score assessing both cognitive and functional ability, using the Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL). CDR-SB is a 5-point scale characterising cognitive and functional performance across 6 domains (memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care). At the first committee meeting, the company used the CDR-SB results of TRAILBLAZER-ALZ 2 to inform the treatment effect of donanemab in the economic model. It provided a scenario analysis exploring the impact of using the iADRS results of TRAILBLAZER-ALZ 2. The EAG noted that European Medicines Agency guidelines – revision 2 (2018) state there is no ideal tool for assessing the efficacy of dementia treatments. A range of tools may be needed and approaches may vary depending on Alzheimer's disease severity. The submissions from the Royal College of Psychiatrists and Association of British Neurologists stated there is no consensus on the best outcome to use to measure treatment response. The Royal College of Psychiatrists noted that iADRS is a newer outcome that is not well established in NHS practice. The EAG noted that a range of measures are used in Alzheimer's disease clinical trials but the Mini-Mental State Examination (MMSE) is the only measure widely used in clinical practice. The EAG advised that CDR-SB adequately reflects how cognition and function are assessed in people with Alzheimer's disease in clinical practice, and it captures factors important to people living with Alzheimer's disease and their carers. The clinical experts agreed that CDR-SB is a validated measure that was reasonable to use in the model. The EAG agreed with the company that CDR-SB was appropriate to inform the treatment effect of donanemab in the economic model. It noted there is also value in exploring iADRS. The committee was aware there would need to be good reasons to justifying modelling a secondary endpoint to reflect clinical effectiveness. The committee noted that the

company's modelled health-state boundaries were defined by CDR-SB score (see section 3.11). So, using CDR-SB to model donanemab's treatment effect is a consistent approach that avoids mixing different clinical outcome measures in the modelling. The EAG used the CDR-SB results from the pooled analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ in its base case. The company stated the hazard ratios for treatment effects in the UK eligible population are confidential so they cannot be reported. The committee decided that both CDR-SB and iADRS measure features of cognition and function that are relevant to the decision problem. The committee concluded it was acceptable to use CDR-SB in the model. It also concluded that it preferred the EAG's approach that used the pooled analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ in the model.

Risks of bias

3.9 For the first committee meeting, the company did a risk-of-bias assessment for TRAILBLAZER-ALZ 2. This gave an overall judgement of 'some concerns' of bias. These were related to possible study unblinding because of the occurrence of ARIA events. The EAG explained that people who had ARIA events and their carers might predict they were having donanemab not placebo and this could affect their CDR-SB responses. The EAG's assessment gave occurrence of ARIA events or infusion-related reactions a 'high risk' of bias (the same as its overall judgement of risk of bias). The EAG advised that this means there is uncertainty in how accurate the treatment-effect estimates are. They could be overestimated or underestimated. At clarification, the company provided a sensitivity analysis of CDR-SB and iADRS outcomes. The EAG noted that its risk-of-bias assessment would apply to both TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. It advised that the company should do the sensitivity analysis based on a meta-analysis of the 2 trials for CDR-SB (see section 3.5). It would also like to see the same analysis done for iADRS. The EAG asked the company to provide economic model scenario analyses using the alternative hazard ratios for

disease progression with censoring for ARIA and infusion-related reactions. In response to the draft guidance the Faculty of Public Health noted that censoring for adverse events will correct for possible study unblinding, but it will exacerbate the attrition bias. So, only people who are doing well on treatment are included in the analyses at later time points. They considered that the company should report the treatment effects stratified by adverse-event type. At the second committee meeting, the company produced hazard ratios for disease progression with censoring for ARIA and infusion-related reactions for the UK eligible population for TRAILBLAZER-ALZ 2 and for a pooled analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. The company stated these results are confidential so they cannot be reported here. The EAG noted that it was reassured that if the occurrence of ARIA events did cause participants or their carers to predict they were having donanemab this did not have a substantial impact on the CDR-SB or iADRS outcome. It added that the summary of product characteristics for donanemab states that when dosing is suspended for symptomatic or radiographically diagnosed moderate or severe ARIA events, it may be resumed if an MRI demonstrates the events have resolved or stabilised, guided by clinical judgement. So, the EAG preferred to use the CDR-SB results without censoring, from the pooled analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ in its base case (see section 3.8). The risk-of-bias assessments presented at the first committee meeting also looked at bias caused by missing outcome data. The company's assessment gave a 'low' risk of bias and the EAG's rating was 'some concerns'. At clarification, the company provided sensitivity analyses of CDR-SB and iADRS outcomes of TRAILBLAZER-ALZ 2. These were for the full ITT population with imputation of missing values, assuming missing at random or not at random, to test the robustness of the primary analyses. The EAG was satisfied with the analyses presented. It noted that these showed donanemab led to less of a decline in cognition and function scores than placebo. The company considers these results confidential so they cannot

be reported here. The committee concluded there were risks of bias in the trial results. It decided that having ARIA events or infusion-related reactions could affect how patients and their carers scored clinical outcomes, which leads to uncertainty in the treatment-effect estimates. It also concluded that the company had explored this and the committee was satisfied it did not have substantial impact on the CDR-SB or iADRS results.

Subgroup effects by standard care treatment

3.10 The decision problem identified that non-pharmacological treatments are used by people with mild cognitive impairment caused by Alzheimer's disease, and acetylcholinesterase inhibitors are used by people with mild dementia caused by Alzheimer's disease. The EAG noted that treatments used alongside donanemab in the trials were different to those specified in the decision problem and by the EAG's clinical expert opinion of NHS clinical practice. It also noted that people entering the trials had higher than expected use of acetylcholinesterase inhibitors or memantine (about 60%). One of the EAG's clinical experts estimated that in UK clinical practice, a minority (below 20%) of people with mild cognitive impairment caused by Alzheimer's disease have acetylcholinesterase inhibitors and none have memantine. At clarification, the company provided a subgroup analysis that explored the effect of baseline medication use (yes or no) on iADRS and CDR-SB. It explained that change from baseline iADRS and CDR-SB scores at week 76 were not significantly different between people using acetylcholinesterase inhibitors and memantine and those not. The EAG noted that based on the results of these analyses, baseline medication use is not expected to affect the cost-effectiveness estimates for donanemab. In response to the draft guidance, the Faculty of Public Health suggested that the higher-than-expected use of acetylcholinesterase inhibitors or memantine is relevant for the generalisability of the trial results. The committee noted that higher than expected levels of standard-care treatments were used by people in the trials and some of this was off-label. It concluded that this led to

uncertainty but overall it was satisfied this did not have an important effect on the trial results.

Economic model

Company's model structure

3.11 The company developed a Markov model with 5 mutually-exclusive health states to estimate the cost effectiveness of donanemab compared with placebo. There was a single model applying to both people in the community setting and in residential care. The health states were defined by MMSE score as mild cognitive impairment caused by Alzheimer's disease, mild dementia caused by Alzheimer's disease, moderate dementia caused by Alzheimer's disease, severe dementia caused by Alzheimer's disease and death. The health-state boundaries were defined by CDR-SB score. People were modelled to stay in their current health state or move to a more severe health state or the death state, which was absorbing. People could start donanemab (see section 3.12) and be on or off treatment in the model in the mild cognitive impairment or mild dementia caused by Alzheimer's disease health states. Transition probabilities for people moving to more severe stages of disease were based on the National Alzheimer's Coordinating Centre Uniform Dataset (NACC UDS). An annual risk of residential care by health state was applied. This was based on NACC UDS data from Spackman et al. 2012 in the company's original base case. Clinical experts advising the EAG advised that values from the European GERAS study (Belger et al. 2019) were more suitable, including because it estimated a higher rate of residential care for people with severe dementia caused by Alzheimer's disease. The EAG noted that the GERAS study included UK patients. So, it preferred to use this study for annual risk of residential care. The company updated its approach at the second committee meeting to use the same source as the EAG for annual risk of residential care. Adverse events from TRAILBLAZER-ALZ 2 incorporated into the model were ARIA events, hypersensitivity, anaphylactic reactions and injection-related

reactions. Disutility values were applied for ARIA and anaphylactic reactions. The company also applied an additional risk of mortality because of treatment with donanemab to the first cycle. The model had a 6-monthly cycle length with half-cycle correction and a lifetime time horizon. The committee noted that it would have liked to see disaggregated, discounted and undiscounted model results for the individual health states, both from the company and the EAG, to understand more about differences between their model results. The committee decided that the company's model structure reflected health states relevant to the decision problem. It concluded that the model structure was acceptable for decision making and the company's updated source for annual risk of residential care was also acceptable.

Model starting proportions

3.12 At the first committee meeting, the company assumed 20.4% of people in the model started donanemab in the mild cognitive impairment health state and 79.6% started in the mild dementia caused by Alzheimer's disease health state. The company noted that these starting proportions were informed by the overall population of the TRAILBLAZER-ALZ 2 trial. At the second committee meeting, the company changed the model starting proportions so that 70% of people started donanemab in the mild cognitive impairment health state and 30% started in the mild dementia caused by Alzheimer's disease health state. The company stated that it made this change because the donanemab marketing authorisation requires people to stop treatment once they progress to moderate dementia caused by Alzheimer's disease. It noted that clinical expert advice to the company was that clinicians would be more likely to start treatment with donanemab earlier and less likely to risk starting in the later stages of mild dementia caused by Alzheimer's disease, to avoid the risk of having to apply the stopping rule. The company's clinical experts suggested that patients and their families would find it distressing to stop treatment before 18 months because of progression to moderate dementia caused by Alzheimer's disease. They also considered that with

more people starting treatment earlier it would ensure that, as far as possible, patients would be able to have the full course of donanemab. The company presented emerging real-world data on use of lecanemab outside the UK, which gave a range of estimates for the proportion of people starting lecanemab with mild cognitive impairment. The company updated its model starting proportions in line with those reported in a US community-based healthcare system study of lecanemab use (n=234; Kile et al. 2024): 70% mild cognitive impairment and 30% mild dementia caused by Alzheimer's disease. The company explored alternative estimates in scenario analyses. The EAG stated that in its base case it would prefer to keep the evidence source for the starting distribution of patients in the model the same as that used for the effectiveness data. So, the EAG wanted to use the proportions from the combined analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ for the UK eligible population. But these data were not reported by the company. So, the EAG maintained the proportions from TRAILBLAZER-ALZ 2 trial in line with the original EAG (and company) base case. The NHS England clinical and commissioning expert noted that the company's updated assumption that 70% of people starting donanemab have mild cognitive impairment is unlikely to reflect the case mix of people currently using NHS memory services. The expert stated that in 2023, in a cohort of more than 6,000 people using memory services, 65% had all-cause dementia and of these 17% had mild cognitive impairment (approximately one-quarter). The expert noted that 30% of people using memory services had dementia caused by Alzheimer's disease but the proportion of people with mild cognitive impairment caused by Alzheimer's disease is not known. The expert suggested it would be a big change if most people using NHS memory services presented with mild cognitive impairment and this was very unlikely in the short term, and if it occurred would take time. The committee noted that the proportion of people with mild cognitive impairment or mild dementia caused by Alzheimer's disease in the UK is uncertain and likely to change. It decided that the company's assumed

model starting proportions for people with mild cognitive impairment did not reflect what is currently seen in NHS memory services. It is also decided that even if the proportions assumed by the company could be reached in practice, it is highly uncertain when this would be. The committee decided that the starting proportions should be aligned with the clinical data and that moving away from these would not be consistent with the rest of the model. It noted that changing the model starting proportions had a large impact on the incremental cost-effectiveness ratio (ICER) for donanemab. It noted that the ICER produced by company's updated base case (with updated model starting proportions) almost doubled when the original model starting proportions based on TRAILBLAZER-ALZ 2 were used. The committee concluded that they preferred the model starting proportions assumed to be based on the TRAILBLAZER-ALZ 2 trial, which informed the company's clinical evidence.

Mortality

3.13 At the first committee meeting, the company assumed that the risk of death for people in the mild cognitive impairment health state was assumed to be the same as the general population (hazard ratio of 1). The EAG's clinical experts advised there was not agreement on whether people with mild cognitive impairment caused by Alzheimer's disease have the same risk of death as the general population or higher. The company also applied a single hazard ratio for mortality of 2.55 to the mild, moderate or severe dementia caused by Alzheimer's disease health states based on dementia-related mortality data from the Office for National Statistics (2020 to 2021). This assumed that people in these health states had a 2.55-times higher risk of death than the general population, but that the risk did not worsen with Alzheimer's disease severity across these health states. The company explained at the first committee meeting that it took this approach because it did not want to model a survival benefit for donanemab with people staying in less severe health states for longer and having a lower mortality risk than people

moving to more severe health states. The EAG noted that published evidence shows that mortality increases as Alzheimer's disease progresses and this was applied in previous cost-effectiveness studies of donanemab. These studies also assumed that people with mild cognitive impairment caused by Alzheimer's disease had a higher risk of mortality than the general population (hazard ratio of 1.61 in Ross et al. 2022 and 1.82 in Lin et al. 2022). At clarification, the company provided a scenario in which mortality increased across the mild, moderate or severe dementia caused by Alzheimer's disease health states based on NACC UDS data. The committee noted that in the scenario, the risk of death in mild or moderate dementia health states was lower than the value used in the company's original base case. The EAG advised the committee that the company's scenario values were not plausible because the mortality risk was higher for mild dementia caused by Alzheimer's disease than moderate dementia caused by Alzheimer's disease. The company commented that the 95% confidence intervals (CI) of these hazard ratios overlapped, indicating they were not significantly different. At the second committee meeting, the company updated its base case using the NACC data, which incorporated variable mortality risk by Alzheimer's disease severity. The updated hazard ratios for mortality were 1.79 (CI 1.54 to 2.09), 1.75 (CI 1.42 to 2.14) and 3.41 (CI 2.87 to 4.07) for mild, moderate and severe dementia caused by Alzheimer's disease health states respectively. The committee noted that the EAG explored a broad range of published evidence in selecting its preferred mortality hazard ratios. The EAG's base-case values were from Crowell et al. 2023, which used NACC data in a subgroup of people aged 80. This was to approximate for the model starting at age 73. The EAG's hazard ratios for mortality were 2.4 (CI 1.68 to 3.33), 3.1 (CI 2.44 to 3.94) and 6.6 (CI 4.82 to 9.07) for mild, moderate and severe dementia caused by Alzheimer's disease health states respectively. The committee noted that the EAG's preferred hazard ratios increased with disease severity and that the confidence intervals for mild and moderate dementia health states overlapped. The

clinical experts advised that the EAG's assumption of a notable increase in risk of death in people with severe dementia caused by Alzheimer's disease was appropriate. The committee noted the lack of trial evidence about whether treatment with donanemab impacts mortality risk. It noted that epidemiological studies show an association between dementia and death. During the second meeting, the committee noted that it had not been provided with any evidence from the company about whether treatment with donanemab was expected to prolong the life of people with Alzheimer's disease. The clinical experts advised that patients in the more severe stages of dementia caused by Alzheimer's disease may not be able to communicate their needs and this makes it difficult to identify and manage concurrent illnesses. They explained that cognitive and clinical decline leads to an increased risk of death that is linked to a loss of function. This is not usually expected in mild cognitive impairment or mild dementia caused by Alzheimer's disease. But in moderate or severe dementia people develop urinary tract infections, pneumonia and pressure sores but cannot express their needs and so are more likely to die from these illnesses. The clinical experts were less certain how different the mortality risk would be between people with mild or moderate dementia caused by Alzheimer's disease. They noted that people at these stages can be reasonably independent; for example, travelling to appointments alone. But they acknowledged there is variability between people and progression of Alzheimer's disease is not linear. The EAG noted that the company's values for mortality risk in mild or moderate dementia caused by Alzheimer's disease applied in its updated base case were lower than reported in all of the published sources that the EAG identified. The company noted that in the EAG's source for mortality risk there was a lack of amyloid testing, so some people with non-Alzheimer's disease dementia may have been included. It noted that because non-Alzheimer's disease dementia may be associated with a higher risk of death, the Crowell et al. values may overestimate mortality in Alzheimer's disease. The EAG suggested that both Alzheimer's disease and non-Alzheimer's

disease dementia could have been misclassified particularly in mild cognitive impairment. So, mortality may be underestimated or overestimated. The company noted that for its values the reference cohort was mild cognitive impairment. But for the EAG's values the reference cohort was the general population, which suggests the EAG's values could be too high. The company also stated that because the analysis used to derive its preferred values considered the cumulative effect of time spent across the different disease stages, this more closely reflected how the risk of mortality was implemented in the model. The committee decided there is uncertainty about the risk of death across Alzheimer's disease severities. It agreed that people in the more severe stages of Alzheimer's disease are more at risk of dying than people in the less severe stages of the disease, so preferred this to be modelled. But it acknowledged that applying this assumption in the model meant that people having donanemab were modelled to live longer than those not having it, which is not based on evidence. The committee concluded that the EAG's approach was based on recent evidence that was adjusted by age to reflect the population modelled for donanemab. It also concluded that the EAG's values were consistent with other published studies and clinical expert opinion about how the risk of death changes across different stages of Alzheimer's disease. So, it preferred to use the EAG's mortality values for decision making.

Treatment duration

3.14 The marketing authorisation for donanemab states that treatment should continue until amyloid plaques are cleared as confirmed using a validated method up to a maximum of 18 months. Based on this, the company's model assumed 90% of people stopped donanemab after a fixed duration of 18 months. The other 10% of people were assumed to have an amyloid-PET scan at 6 or 12 months and stop donanemab if the scan showed amyloid clearance to less than 24.1 centiloids. People also stopped donanemab on progression to the moderate or severe dementia caused by Alzheimer's disease health states or because of an adverse

event. The EAG's clinical experts noted there is limited infrastructure in place in the UK to monitor amyloid clearance by PET scan. So, at the first committee meeting the EAG assumed all people would have donanemab for up to 18 months. The NHS England submission at the first committee meeting estimated that 15% of people would have an amyloid-PET scan and most people would continue donanemab treatment for 18 months. The committee decided at the first meeting that it would like to see further information from the company and NHS England that fully explains the estimated proportion of people who stop donanemab before 18 months based on amyloid-PET scan results. At the second committee meeting, the company stated that although availability of PET scanners in the UK is limited it is likely to increase in the future. It considered the EAG was incorrect to assume no people would be scanned for amyloid clearance with the possibly of stopping treatment early. The company noted that, if recommended, use of donanemab is expected to be within specialist sites that already have PET scanning capability and the necessary infrastructure in place. In response to the draft guidance, NHS England provided a revised submission that presented 2 treatment duration scenarios. With the availability of PET scanning at 6 and 12 months, scenario 1 assumed that 32% of people might stop donanemab early, which would lead to an average treatment duration of about 62 weeks (or almost 15 months). It noted that this scenario was dependent on sufficient radiotracer supply being secured to do the PET-CT scans and PET-CT scanning capacity, which will also be needed in diagnosing patients. Without the availability of PET scanning to monitor amyloid, NHS England's scenario 2 assumed 100% of people would have donanemab for 18 months. This may be an overestimate because it does not include stopping for other reasons. NHS England noted that scenario 2 was not dependent on radiotracer availability or PET-CT scanning capacity. It also suggested that the expected treatment cost per patient would be lower with PET scanning than without it. The EAG noted that NHS England used evidence provided by the company and the donanemab marketing

authorisation as the basis for its modelling of donanemab treatment duration. At the second committee meeting, the NHS England commissioning expert suggested that PET scanning capacity would need to be built up to deliver scenario 1 with PET scanning to monitor amyloid. The expert noted that the biggest issue with reaching capacity could be securing radiotracer supply, which needs same-day manufacture. They noted that NHS England's preference is that PET monitoring could be done, but this would need to prioritise PET use in diagnosis and then be rolled out for monitoring when enough capacity was in place. They also noted that uptake of PET monitoring was uncertain. For its updated base case, the EAG decided it was reasonable to assume that use of PET scanning to monitor amyloid would not be zero. The EAG considered that the company's preferred assumption fell somewhere between the 2 scenarios presented by NHS England. So, it updated its base case in line with the company's approach. The committee concluded there is uncertainty about the expected availability of PET scanning and radiotracer supply for monitoring brain amyloid, and about how much of this monitoring would be done. It also concluded that the company and EAG's updated assumption that 10% of people stopped donanemab before 18 months because of amyloid clearance was acceptable for decision making.

Long-term assumptions for full treatment effect

3.15 At the first committee meeting, the company explained that it modelled treatment exposure and response simulations based on data from 4 donanemab trials to predict a rate of amyloid reaccumulation (2.8 centiloids per year) that could inform donanemab's long-term treatment-effect assumptions. Based on observed amyloid levels in TRAILBLAZER-ALZ 2 at 76 weeks, the company estimated it would take about 3.5 years to return to amyloid positivity (24 centiloids or more) after the last donanemab dose. So, the company assumed that the full treatment effect of donanemab on lowering the risk of Alzheimer's disease progression lasted 5 years in the model, including on and off treatment

periods. The committee noted that at the time of the first committee meeting no trial evidence was available on the clinical effectiveness of donanemab beyond 18 months. Also, there was no trial evidence on the rate of amyloid reaccumulation beyond 18 months and whether this is different from the natural course of Alzheimer's disease. The committee also noted that change in amyloid is a disease biomarker but not a measure of clinical effectiveness. The company noted that in TRAILBLAZER-ALZ 2, amyloid clearance (see section 3.14) was seen in 29.7% of people who had amyloid-PET screening at 6 months and 36.4% of people who had amyloid-PET screening at 12 months (total 66.1%). This was compared with less than 1% of people having placebo. The company explained that a continued benefit of donanemab was seen in people who stopped early because of amyloid clearance, with the change in iADRS and CDR-SB curves for the 2 arms continuing to separate from 6 or 12 months to 18 months in the trial. The committee noted that these observations were in the subset of people with the best response to donanemab treatment as measured by amyloid clearance. So, they are not generalisable to all people having donanemab and most people in the trial could not stop treatment early because of amyloid clearance. The committee agreed it is plausible that the amyloid-lowering effects of donanemab could translate into some continued lowering of the risk of progression after treatment stops. But it noted the company had not provided evidence linking reduced amyloid levels after donanemab treatment with clinically relevant changes in cognition and function in Alzheimer's disease. At the first meeting, the committee encouraged the company to provide further evidence supporting this link. The EAG's clinical experts advised that the company's approach to modelling long-term treatment effect was speculative. The EAG preferred to assume a less sustained treatment effect of donanemab after stopping. This included that the full effect on lowering the risk of progression continued for 1 year after stopping treatment. The EAG noted that its approach was based on the available trial evidence, which was that people who stop

treatment at 6 months continue to see a benefit for 1 year. So, the full treatment effect of donanemab on and off treatment was assumed to last 2.5 years in the EAG's base case. The clinical experts advised there is great uncertainty about the potential long-term treatment effects of donanemab. They noted that whether the reduced risk of decline in cognition and function seen in the trial is maintained after stopping treatment and, if so, for how long are important unanswered questions.

At the second committee meeting, the company recalculated the estimated time it would take to return to amyloid positivity after the last dose of donanemab to be 4 years, based on the UK eligible population of TRAILBLAZER-ALZ 2. So, the company extended its assumption for the duration of the full treatment effect of donanemab on and off treatment to 5.5 years in the model. The company also presented evidence from 3 studies that it considered linked defined amyloid plaque levels with risk or timescale of clinical progression or functional decline. At the second committee meeting, the EAG suggested that the link between amyloid clearance and short-term clinical benefit has been demonstrated in TRAILBLAZER-ALZ and other amyloid targeting therapy trials. The EAG also stated that its assumption that the full treatment effect continued for 1 year after stopping treatment was consistent with the limited trial evidence available. The NHS commissioning expert noted that it was uncertain whether the company or EAG's different assumptions were generalisable to people who might have donanemab in the NHS, because people might be older and more likely to have a mixed brain pathology that is causing dementia. The committee acknowledged that the longer-term clinical effects of donanemab are unknown. It decided that the company's and EAG's modelling of long-term treatment effect is highly uncertain. The committee concluded that it preferred the EAG's assumption that the full treatment effect continued for 1 year after stopping treatment. It noted this was based on the limited clinical trial evidence available.

Long-term assumptions for waning

3.16 At the first committee meeting, the company noted that clinical opinion suggested it was not plausible that the treatment effect of donanemab would be immediately lost upon return to amyloid positivity (24 centiloids, see section 3.15). So, the company assumed that donanemab's treatment effect gradually waned to zero over a further period of 5 years. This was modelled as a linear decline to zero in the amount by which the risk of Alzheimer's disease progression was lowered. The committee noted that the company presented no trial evidence about how donanemab's treatment effect might wane after stopping. At the first committee meeting, the EAG preferred to assume a duration of treatment-effect waning of 2.5 years. It noted that this, combined with its assumed 1-year full effect after stopping, was in line with the company's original model prediction that amyloid would take 3.5 years to reaccumulate to 24 centiloids (section 3.15). The company commented that in the EAG's approach, all benefit of donanemab in lowering of the risk of progression ends once the amyloid positivity threshold of 24 centiloids or more is reached. But this threshold is low, being about one-quarter of the level of amyloid seen at baseline in the trial (more than 100 centiloids). The clinical experts thought it likely that the benefits of treatment with donanemab would reduce over time. Based on the proposed action of donanemab as a treatment that binds to amyloid and promotes its removal from the brain, they advised that a sudden end to its treatment effect was unlikely. The clinical experts noted that in people with low-to-moderate tau protein levels in TRAILBLAZER-ALZ 2, who represented a less severe cohort compared with the overall population used in the model, there was less decline in cognition and function over time. The experts suggested that this evidence in people who are still having treatment indicates that the benefits of donanemab decrease as Alzheimer's disease becomes more severe. At the second committee meeting, the company presented evidence from studies that linked defined amyloid plaque levels with risk or timescale of clinical progression or functional decline. The people in these studies were cognitively normal, not diagnosed with Alzheimer's

disease. The company noted evidence that in people with amyloid levels between 26 to 50 centiloids, there was little clinical progression and functional decline until after 4 to 5 years of follow up. So, it extended its assumption for gradual waning to occur over 9 years based on the time it would take to reach an amyloid level of 50 centiloids assuming the predicted rate of amyloid reaccumulation of 2.8 centiloids per year (section 3.15). The EAG noted this meant donanemab was assumed to have a total duration of effect (full or waned) of 14.5 years in the company's updated model, based on a maximum 18-month treatment period. At the second committee meeting the EAG updated its waning assumption based on the evidence presented by the company. The EAG noted that because clinical progression and functional decline only occurred after 4 to 5 years of follow up in people with amyloid levels between 26 to 50 centiloids, it assumed a duration of treatment-effect waning of 5 years. Using the EAG's updated approach, donanemab was assumed to have a total duration of effect (full and waned) of 7.5 years in the model. The EAG noted that applying its preferred long-term assumptions for full and waned treatment effect to the company's updated base-case model led to a large increase in the ICER for donanemab. The committee concluded that the treatment effect waning after stopping donanemab is unknown. So, the company's and EAG's modelling of long-term treatment waning is highly uncertain. It noted that because of the mixed pathology of Alzheimer's disease, which may include increasing tau levels, it is uncertain whether waning would be linear. The committee decided the company's approach that assumed waning for 9 years and a total duration of donanemab effect (full and waned) of 14.5 years was implausible. It concluded that based on the evidence presented it preferred the EAG's updated assumption for waning. It also concluded that this approach may be optimistic.

Utility values

People living with Alzheimer's disease

3.17 The company explained that no EQ-5D data were collected in TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. Health-related quality of life data were instead collected using the Quality of Life in Alzheimer's Disease questionnaire in a subset of people in TRAILBLAZER-ALZ 2. In the company's model, the utility value for people in the mild cognitive impairment caused by Alzheimer's disease health state was assumed to be the same as the general population. Utility values for people in the mild, moderate or severe dementia caused by Alzheimer's disease health states were from a systematic literature review and meta-analysis by Landeiro et al. 2020. This reported pooled estimates of patient utility values assessed both by the people living with Alzheimer's disease and their carers. The EAG noted that the pooled estimates combined EQ-5D utility values calculated using different countries' value sets to derive a single utility value for each health state. It explained that the company's approach was outside the NICE reference case because the values were not from a representative sample of the UK population. The EAG preferred to use EQ-5D utility values for patients from the GERAS study (Wimo et al. 2013) for the mild, moderate or severe dementia caused by Alzheimer's disease health states in its base case. The EAG noted that the GERAS study was the largest single UK study identified in the company's systematic literature review and was larger than any single UK study included in the Landeiro et al. meta-analysis that the company preferred. In the GERAS study, carers completed the proxy version of EQ-5D for the patient. The study was done in the UK, France and Germany but used a UK value set to derive the utilities. The EAG provided a scenario based on the UK-only subpopulation of GERAS. The EAG assumed the utility value for people in the mild cognitive impairment caused by Alzheimer's disease health state was the same as the general population. The committee noted that the EAG's utility values showed less of a decline when moving to the moderate and severe dementia caused by Alzheimer's disease health states than the company's preferred values. It noted that the EAG's values used estimates relevant to the UK.

The committee noted that both the company's and EAG's utility values for patients included proxy-reported values provided by carers. It noted that NICE's manual for health technology evaluations states that health-related quality of life should be measured directly by people with the condition being treated. But, when it is not possible to get these measurements directly from people, they should come from people acting as their carer. It understood that people with Alzheimer's disease may become unable to complete quality-of-life questionnaires because of cognitive decline, and that it may be suitable to use proxy measures. But it noted evidence that there was poor agreement between quality of life estimated by people with Alzheimer's disease and by carer proxy. The committee also noted concerns that self-reported quality of life may not be an accurate reflection of quality of life, partly because people adapt to the symptoms of their condition. So, they are not recording their quality of life relative to true full health. At the first meeting, the committee asked to see further information from the company and EAG on their approaches to utility values, which consider the concerns and the uncertainty they created. At the second committee meeting, the company and EAG maintained their preferred uses of proxy values for patient utilities. The clinical experts stated that there was a disappointing lack of knowledge about patient utility values in Alzheimer's disease and whether proxy values were reasonable. In particular, more work could be done in understanding what matters to people with mild cognitive impairment, while their symptoms are still mild and they could be expected to have insight into their own condition. The experts agree that from mild to moderate dementia caused by Alzheimer's disease people might lose insight so would have less understanding of themselves. The committee decided that proxy values for patient utilities presented by the company and EAG are highly uncertain. It noted that in a scenario analysis, when the EAG explored the impact on its preferred base case of changing the utility values to those preferred by the company, this had a large impact on the ICER for donanemab. After consultation the company provided a re-analysis of the GERAS utility

values. The company's re-analysis adjusted the MMSE score ranges used to define mild, moderate and severe Alzheimer's disease health states to match the score ranges used in the model. The committee noted that this produced patient utility values for mild, moderate and severe Alzheimer's disease that were between those of the company and EAG preferred base case values. The EAG was unable to critique this approach because the analyses were received shortly before the committee meeting. The committee concluded that based on the limited evidence presented, it preferred to use the GERAS values updated to aligned with the MMSE categories used in the model because they are relevant UK estimates.

Carers

3.18 The company decided that EQ-5D might not be sensitive enough to measure the health-related quality of life of carers for people living with Alzheimer's disease. So, it preferred to do 2 vignette studies to derive carer utilities using a time trade-off approach. One vignette study informed the health-state utilities for carers of people with mild cognitive impairment or mild dementia caused by Alzheimer's disease in community and residential care settings, and for moderate dementia caused by Alzheimer's disease in the community setting. It was based on interviews with 304 people in the UK general population. The other vignette study informed the health-state utilities of carers of people with moderate dementia caused by Alzheimer's disease in the residential care setting and severe dementia caused by Alzheimer's disease dementia in community and residential care settings. It was based on interviews with 100 people in the UK general population. The EAG advised that the company had provided insufficient evidence to justify the conclusion that the EQ-5D is an inappropriate measure of health-related quality of life for carers of patients with Alzheimer's disease. The company assumed there were 1.8 carers per patient when applying the carer utilities in the model. The company explained this was based on people living with Alzheimer's disease in the GERAS study having an average of 1.8 carers. The EAG noted that applying the same quality-of-life estimates for all carers was

likely to be unrealistic. The EAG preferred to use EQ-5D scores from the GERAS study, which were reported for the primary carer (Reed et al. 2017). The EAG noted that in this study the utility value for carers of people with mild dementia caused by Alzheimer's disease was higher than in the general population matched for age and gender distribution. So, the carer utilities for both the mild cognitive impairment caused by Alzheimer's disease and mild dementia caused by Alzheimer's disease health states were assumed to be the same as the general population. For the moderate and severe dementia caused by Alzheimer's disease health states, the EAG adjusted the general-population utilities based on the relative decrement between the health states observed for carer utilities in the GERAS study. The committee noted that the EAG's utility values showed less of a decline in the moderate and severe dementia caused by Alzheimer's disease health states than was seen using the company's preferred values in these health states. The EAG noted that carer utilities from the GERAS study were reported for the primary carer. It noted that although other carers of people living with Alzheimer's disease may experience a loss in quality of life, there was a lack of published evidence on the utilities for secondary carers. At the first committee meeting the EAG used a simple approach that assumed only 1 carer when applying the utilities. The EAG explained that because applying 1.8 carers in a scenario with its preferred utilities did not have a big impact on the cost-effectiveness results, it did not explore this further. The committee noted clinical expert comments that some people living with Alzheimer's disease can be reasonably independent in the earlier stages (see section 3.13). So, the EAG's assumption that carer utility in mild cognitive impairment caused by Alzheimer's disease and mild dementia caused by Alzheimer's disease health states is the same as the general population could be reasonable. The committee noted that the EAG's approach of assuming 1 carer was consistent with its values being for the primary carer.

At the second committee meeting, the EAG maintained the caregiver utility values from GERAS but updated its assumption for the number of caregivers to 1.2. The company noted that its assumption of there being 1.8 carers came from the GERAS study. The clinical experts commented that the carer role for people with Alzheimer's disease is crucial but highly variable between patients. They suggested that the change in caregiver utility across the EAG's values for increasing disease severity may be too small and a higher impact would be expected for severe dementia caused by Alzheimer's disease. This may especially be the case when considering sole carers. The committee noted that the change in caregiver values across Alzheimer's disease health states presented by the company were large. It noted that for a spouse with the patient living in the community, the company approach assumed that caregiver utility reduced by more than half as the patient moved from mild cognitive impairment to severe dementia caused by Alzheimer's disease. The committee recalled the experiences of carers looking after their family members with severe dementia caused by Alzheimer's disease. It noted that a larger impact on caregiver utility might be expected particularly in severe dementia caused by Alzheimer's disease. But it was unclear from the study presented how that would be distributed over the population without more robust evidence. The committee decided that it had not been presented with any new evidence that convinced it to change its decision from the first committee meeting; that is, using the EAG's preferred approach to calculating carer utility values from GERAS. It noted this was based on a large study giving UK relevant estimates and appeared reasonable. The committee also decided that, in line with the GERAS study, assuming 1.8 caregivers is appropriate. The committee concluded that it preferred to use the EAG's source for caregiver utility values and assume 1.8 caregivers (which the company preferred). It also concluded the utility values for caregivers of people with Alzheimer's disease are highly uncertain.

Costs

Infusion costs

3.19 The company's model assumed that the administration cost of each donanemab infusion was £208. This was based on the SB12Z tariff cost in the 2021 to 2022 National Tariff Payment System. The code relates to a simple parenteral chemotherapy at first infusion. The company explained that this code took account of donanemab being given over 1 hour as a 30-minute infusion followed by 30-minute observation. The EAG assumed the same infusion cost for donanemab as the company in its base case. It noted that submissions from NHS England at the first committee meeting identified a different infusion cost that it considered was more suitable. The EAG explained it had not been able to fully verify NHS England's proposed costs and preferred to apply them in a scenario than in its base case. The NHS England infusion cost was £565, based on the WD02Z healthcare resource group (HRG) code estimate from 2019 to 2020 and uplifted to current prices. The code is titled 'Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider'. NHS England explained that this is the HRG code that would most likely be recorded when a person has a donanemab infusion. It reflects the actual amount that service providers will currently be paid to provide a donanemab infusion. NHS England explained that the cost it calculated may be conservative because there is no single published price. So, it used the average across multiple indications, not just for Alzheimer's disease, which is a higher cost. At the second committee meeting, NHS England recommended using the infusion cost for coronavirus monoclonal antibodies (£432) because this cost was estimated using a bottom-up costing approach based on real-world costs. It noted that it had submitted the same cost for consideration in the appraisal of lecanemab. It advised against using the simple parenteral chemotherapy infusion cost because donanemab is more complex to prepare, has the potential for more adverse reactions and people might have more complex needs. The company stated that donanemab infusion is not associated with a higher

rate of infusion-related reactions than chemotherapy. The EAG incorporated the £432 NHS England infusion cost to its updated base case. It noted that in a scenario analysis using the company's preferred infusion cost this had a moderate impact in reducing the EAG's ICER for donanemab. In response to the draft guidance, NHS England advised against putting too much emphasis on only 1 element of treatment costing. It stated that NHS pricing typically charges based on an average cost principle, which mostly use published tariffs. Actual resource requirements might differ from the average for an eligible cohort (standard tariffs). The committee noted that this average cost principle would also apply to costs of scans, tests and appointments and may represent an underestimate of actual costs considering the population covered by this appraisal. Clinical experts noted that if donanemab was recommended, the costs of providing it would become clearer over time. This might include lower costs associated with centres becoming more efficient in giving infusions and streamlining of MRI safety monitoring. They also suggested that if blood-based biomarkers were in routine use there might be less use of PET scanning in diagnosis. The NHS commissioning expert noted that experience from the US was that blood-based biomarkers are currently used in addition to PET scanning, not instead of it. This could increase costs, so NHS England did not include blood-based biomarkers in its costing. The committee noted that the infusion cost for donanemab should reflect the health system resources required for giving an infusion of donanemab. The company noted that the infusion time stated in the marketing authorisation is different for donanemab (at least 30 minutes) than for lecanemab (approximately 1 hour). So, the cost of infusing donanemab should be lower than for lecanemab. The committee noted that applying NHS England's infusion cost led to a moderate increase in the company's updated base-case ICER. The committee noted a lack of transparency on how the cost was estimated and how it related to specific donanemab resource requirements. So, it was unable to determine a preferred cost for use in modelling. The committee concluded that the

most appropriate cost is likely closer to the NHS England estimate than the company's but noted the uncertainties with how it was estimated. It also concluded that it would use both the company and NHS England infusion cost estimates when considering the most plausible ICER range.

Outpatient consultant visits

3.20 At the first committee meeting, the EAG advised the company's estimates for the diagnosis and monitoring of people with early Alzheimer's disease were reasonable. The EAG's clinical experts agreed except for the costing of APOE4 testing, which included the test (£44) but not the cost of an outpatient appointment (£222). The EAG's clinical experts suggested that most carriers of an APOE4 allele would also need some counselling because genetic results are difficult to understand and should be explained to people even if they are not eligible for treatment. One of the EAG's experts said that counselling could be part of a normal outpatient appointment already planned as part of the diagnostic process. The EAG did not include a separate counselling appointment in its base case but explored it as part of a scenario based on submissions from NHS England. The EAG noted that patients do not have outpatient consultant visits for monitoring in the model. At clarification, the company included the option to include 1 outpatient consultant visit per cycle in its model and provided a scenario analysis including this. It explained that it did not adjust its base case because it expected outpatient consultant visits to be covered by the NHS Reference costs included in the model. The EAG disagreed and advised that these needed to be costed separately. So, the EAG added 1 outpatient consultant visit at diagnosis and 1 per cycle during treatment (3 over 18 months) to its base case. The committee noted that the EAG's approach was consistent with clinical expert advice provided to the EAG. At the second committee meeting, the company updated its base case to include 1 outpatient consultant visit at diagnosis and 1 per cycle (6 months) in the model. In response to the draft guidance, the company that makes lecanemab (Eisai) noted that the NHS England model assumed an outpatient visit every 3 months. It noted that it

also included the cost for genetic counselling in its model (£350) for 50% of people testing APOE4 homozygous based on the NHS England submission for the first committee meeting. The committee noted at the second meeting that there was some uncertainty whether outpatient visits for monitoring would be every 3 or 6 months for donanemab. It also noted that genetic testing is a requirement of the marketing authorisation for considering people eligible for treatment with donanemab. Clinical experts stated that genetic counselling is not mandatory when people are already experiencing symptoms of Alzheimer's disease, and instead can be part of the clinical discussion. They added that an important impact of genetic testing is on siblings or children of the person presenting with symptoms. They noted that they would expect a separate appointment with a healthcare professional about sharing the outcome of genetic testing with family members and a follow-up call giving the results. The committee decided that the costs of outpatient consultant visits should be included for diagnosis and for monitoring visits in line with the company and EAG approach, although there is uncertainty about how often monitoring would be done. It also concluded that modelling did not capture any additional cost for providing genetic counselling for patients or their families.

Healthcare resource use

3.21 The company's model used health-state costs taken from the Personal and Social Services Research Unit (PSSRU) report for mild, moderate and severe dementia caused by Alzheimer's disease and for residential care. Health-state costs for mild cognitive impairment caused by Alzheimer's disease were taken from the study by Wittenberg et al. 2019. The EAG noted that costs from the PSSRU report were also derived from the Wittenberg study but included unpaid care costs. This is outside of the cost perspective set out in the NICE reference case. The company provided a scenario analysis using costs from the Wittenberg study but not including unpaid care costs. The committee noted at the second meeting that in a scenario analysis this had a large impact on the ICER for donanemab. The EAG preferred to use these health-state costs from

Wittenberg, not including unpaid care costs in its base case. At the first committee meeting, the EAG noted that the company model included a one-off end of life care cost. The EAG explained that healthcare estimates from Wittenberg et al. (used by the company and EAG) already included end of life care costs. So, it removed this one-off cost. For the first committee meeting, the company updated its model to remove a one-off end of life care cost. The committee decided it was not appropriate for the company to include unpaid care costs in its model. It concluded that it preferred the EAG's approach of removing these.

Cost-effectiveness estimates

Committee's preferred assumptions

3.22 The committee concluded that the cost-effectiveness estimates were very uncertain (see section 3.23). It agreed the company's overall model structure is acceptable for decision making (see section 3.11). The committee's preferred assumptions at the second committee meeting were:

- the EAG's model starting proportions for the mild cognitive impairment and mild dementia caused by Alzheimer's disease health states (see section 3.12)
- the EAG's values for mortality (see section 3.13)
- the EAG's long-term treatment-effect assumptions (see sections 3.15 and 3.16)
- the EAG's preferred GERAS study as the source for proxy-reported patient utilities, but adjusting these values to align with the MMSE categories in the model (company's analysis) (see section 3.17)
- the EAG's preferred values for carer utilities from the GERAS study (see section 3.18) but using the company's preferred number of caregivers (1.8), which is also from the GERAS study

- the EAG's approach that removed unpaid care costs from the modelled healthcare resource use (see section 3.21).

Uncertainty in the cost-effectiveness estimates

3.23 The committee acknowledged the remaining uncertainties in the lack of long-term evidence for donanemab and the company and EAG's modelling assumptions. It decided that there remained substantial uncertainty in the cost-effectiveness estimates generated using its preferred assumptions because of uncertainty about the:

- treatment-effect estimates (see section 3.8, 3.9 and 3.10)
- likely proportion of people starting donanemab with mild cognitive impairment or mild dementia caused by Alzheimer's disease (see section 3.12)
- mortality risk that should be assumed in different Alzheimer's disease severities (see section 3.13)
- proportion of people (if any) who would stop donanemab before 18 months based on amyloid-PET scan results (see section 3.14)
- long-term assumptions of clinical effectiveness, noting it is highly uncertain if and for how long the full treatment effect of donanemab is maintained then wanes after stopping (see sections 3.15 and 3.16)
- utility values used in the model (see section 3.17 and 3.18)
- costs including infusion cost (the plausible range was from the company's estimate to the cost for coronavirus monoclonal antibodies shared by NHS England), how many on-treatment monitoring visits would happen and whether a counselling visit should be costed separately for genetic testing (see section 3.19 and 3.20).

Company and EAG cost-effectiveness estimates

3.24 At the first committee meeting, the company provided absolute and proportional quality-adjusted life year (QALY) shortfall estimates in line

with NICE's manual for health technology evaluations. The committee noted that the values did not meet the threshold for a severity weight greater than 1 to be applied to the QALYs in the company and EAG base cases. The cost-effectiveness results presented at the second committee meeting included a revised confidential discounted price for donanemab. The committee noted that the cost-effectiveness estimates were highly uncertain (see section 3.23). The company's deterministic base-case ICER for donanemab compared with placebo was about £12,000 per QALY. The EAG's base-case ICER was about £135,000 per QALY, which is considerably above the range normally considered cost effective for routine NHS use. The committee noted that applying its preferred assumptions (see section 3.22) to the company's updated base case resulted in a plausible ICER range for donanemab that was considerably above the range normally considered cost effective. This was from about £113,000 per QALY using the company's preferred infusion cost to about £126,000 per QALY using the NHS England (and EAG) preferred infusion cost. The company noted that for some combinations of assumptions that include the NHS England infusion cost, donanemab may not be considered cost effective even at very low or zero cost. The committee was aware that section 4.4.16 of the manual states that 'in cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost effective at NICE's normal levels, the committee may consider alongside the reference-case analysis a non-reference-case analysis with the background care costs removed'. But it did not consider this applicable in this evaluation because the non-drug costs largely relate to administration of the treatment rather than the costs of prolonging time in expensive health states. The committee concluded that it could not recommend donanemab for routine use. This was because the most plausible ICER range was likely considerably above the range normally considered cost effective, and because of uncertainty in all the cost-effectiveness estimates. The committee was aware that section 6.2.33 of the manual

states that 'when considering uncertainty, the committee should take into account the likelihood of decision error and its consequences for patients and the NHS.' So, the committee considered the potential benefits and risks to patients based on the level of decision uncertainty and whether this could be mitigated. The committee noted that only a modest benefit to patients was demonstrated in the trial. It also noted that substantial resources would be needed to implement access to donanemab in the NHS and that this may affect the provision of other services (see section 3.27). It decided the decision-risk was too great to recommend donanemab.

Managed access

3.25 Having concluded that donanemab could not be recommended for routine use, the committee considered whether it could be recommended with managed access for treating mild cognitive impairment and mild dementia caused by Alzheimer's disease. The committee noted that the company provided a new managed access submission for the second committee meeting. The company presented ongoing or planned studies that aim to address the uncertainty around the long-term treatment effect. The extension phase of TRAILBLAZER-ALZ 2 would provide up to an additional 36 months of follow-up data for people starting donanemab early compared with a delayed start. This trial phase, which includes UK sites, would also measure the rate of amyloid accumulation over 2 years. Further 18-month follow up data on clinical endpoints would be available from TRAILBLAZER-ALZ 5. The planned TRAILBLAZER-REAL Global study will provide prospective data over 5 years on endpoints including functioning, quality of life, mortality and caregiver burden. The company also proposed collecting real-world evidence on safety and effectiveness through the Platform for Early Alzheimer's in Real Life and the International Registry for Alzheimer's Disease and other Dementias. The company presented ongoing or planned studies that aim to address the uncertainty around the healthcare costs and resource use associated with donanemab treatment in the UK and other data collection programmes.

These were 2 retrospective studies expected to provide data in 2025 and 2027 and the anticipated prospective UK Controlled Access Program for donanemab that was stipulated in the marketing authorisation. The clinical lead for the Innovative Medicines Fund highlighted that the usefulness of data from the extension phase of TRAILBLAZER-ALZ 2 in resolving key uncertainties would be limited by its duration. They noted it was unclear how many people would be followed to the end of the longer-term studies presented. They advised that some uncertainties may not be addressed by further data collection. At the second committee meeting the company acknowledged that the longer-term trial extensions would not provide randomised placebo-controlled data. It explained that it expected to build external control arms to inform longer-term comparisons for people having donanemab. The committee emphasised the need for robust comparative data on the long-term effects of donanemab after treatment ends. It noted the views of the managed access team that ongoing trials could generate further evidence to resolve some uncertainties. But several uncertainties would not be addressed at all by further data collection and some would only be partly addressed. The clinical lead for the Innovative Medicines Fund noted that no NHS-level data collection was proposed beyond baseline characteristics on enrolment, so the most feasible way to gather further data would be through trials. They stated concerns about donanemab meeting the necessary criteria for a recommendation in managed access. Specifically, the ICER range for donanemab incorporating the committee's preferred assumptions was not plausibly cost effective. And there were significant concerns that implementation would lead to considerable burden with or without data collection in the NHS. The committee decided that based on its preferred ICER range (see section 3.24) it was unlikely that donanemab had the plausible potential to be cost effective. It also considered that a key driver of these results was the modest clinical benefit of donanemab. It understood that data collected in managed access from the randomised controlled trials was unlikely to illustrate a substantially greater clinical benefit for donanemab

than estimated in the company or EAG base case. So, the committee concluded that donanemab did not meet the criteria to be considered for a recommendation with managed access.

Other factors

Equality and health inequality issues

3.26 Submissions from the clinical and patient experts during the evaluation identified potential equality and health inequality concerns for consideration. These were presented at the first and second committee meeting and were:

- there is current inequality in getting an Alzheimer's disease diagnosis and accessing care. This would be exacerbated by introducing the complex diagnostic pathway for donanemab. People without a carer who can help them get a timely diagnosis would be among those disadvantaged
- people with Down's syndrome (who have a more than 90% lifetime risk of developing Alzheimer's disease), young-onset dementia or from ethnic minority backgrounds were not fully represented in TRAILBLAZER-ALZ 2. These people are at risk of being excluded from accessing donanemab
- donanemab would need significant increases in NHS capacity for service delivery. Inequalities might increase because existing services that are already under strain would be delivering the treatment. The effect of this would likely be greater for people in deprived socioeconomic circumstances.

The committee noted the concerns raised about getting a diagnosis, accessing care in a new and complex pathway and substantial demand on NHS services. It understood these concerns but noted they were outside of its remit. The committee understood that some people with Alzheimer's disease have Down's syndrome and may be considered disabled under the Equality Act 2010. It also noted that age, sex, family

background and disability are protected characteristics under the Equality Act 2010. The committee agreed that any recommendation should not restrict access to treatment for some people over others on the basis of protected characteristics.

Uncaptured aspects

3.27 Stakeholder submissions during the evaluation identified potential uncaptured benefits and costs of donanemab. The potential uncaptured benefits of donanemab were:

- access to a new potentially disease-modifying treatment such as donanemab could reduce the fear associated with having Alzheimer's disease and is likely to lead to the evolution of clinical care pathways in the NHS and overall improvements in the care provided for patients
- use of proxy-reported patient utility data from the GERAS study may not have captured the more severe cases of Alzheimer's disease because it was done in the community setting
- the impact on the finances and productivity of unpaid carers for people with Alzheimer's disease were not captured in the model. The committee noted that these costs fall outside of NICE's reference case
- donanemab is not eligible for the severity modifier (see section 3.24):
  - people living with Alzheimer's disease typically become dependent on their carer for everyday functioning, which makes the burden on carers an essential aspect of the disease
  - there is a perceived disconnect between NICE's reference case perspective, which can include both patient and carer quality of life, and the calculation of the severity modifier which only includes patient quality of life.

The potential uncaptured costs or harms of donanemab raised were:

- 'false hope' for people who are not eligible for donanemab, or who may find out they are APOE4 carriers and may experience worse outcomes than others
- 'false hope' for people who believe that donanemab is a cure for Alzheimer's disease rather than a treatment that aims to slow disease progression
- burdens on patients and carers associated with treatment including need for lumbar puncture, frequent infusions and MRI scans
- significant increase in demand for NHS primary and secondary care services that may affect the provision of other services
- substantial investment in infrastructure and training for NHS care pathways to be redesigned to accommodate new treatments.

The committee concluded that the uncaptured benefits and costs or harms of donanemab may increase or decrease the most plausible ICER. And it agreed there were significant uncertainties in the company's base case (see section 3.22). So, the committee was unable to reach a conclusion on the effects of uncaptured benefits and costs.

Conclusion

Recommendation

3.28 The committee acknowledged the significant unmet need for treatment options to slow or prevent progression from mild cognitive impairment or mild dementia caused by Alzheimer's disease. It also recalled the high uncertainty associated with the modelling, including in the long-term evidence for donanemab. It noted that the EAG's and company's base cases were associated with uncertainty, and the most plausible cost-effectiveness estimates were considerably above the range normally considered a cost-effective use of NHS resources. The 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. This is in addition to the lack of plausible cost effectiveness and concerns that additional data collection would not resolve the uncertainties. So, it did not recommend donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease in adults who are APOE4 heterozygotes or non-carriers, either for routine NHS use or with managed access.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John and Raju Reddy

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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