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Draft guidance consultation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: October 2024

Note that this document is not NICE's final guidance on this technology. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using donanemab in the NHS in England.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: 20 November 2024
- Second evaluation committee meeting: 15 January 2025
- Details of the evaluation committee are given in section 4

Issue date: October 2024

1 Recommendations

1.1 Donanemab is not recommended, within its marketing authorisation, for treating mild cognitive impairment and mild dementia due to Alzheimer's disease in adults who are apolipoprotein (APO) 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. Treatments for mild dementia caused by Alzheimer's disease include an acetylcholinesterase inhibitor (donepezil hydrochloride, galantamine or rivastigmine). Donanemab would be used at the same time as current treatments at these stages of Alzheimer's disease.

Evidence from clinical trials suggests that cognitive function continues to worsen over time with donanemab added to current treatment, but at a slower rate than with placebo. But there is not enough evidence on the long-term effects of donanemab.

There are substantial uncertainties in the economic model, including:

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

Because of the uncertainties, it is not clear what the most likely cost-effectiveness estimate is for donanemab. But it is likely to be above what NICE normally considers an acceptable use of NHS resources. So, donanemab is not recommended for routine use.

NICE has asked the company and NHS England to provide additional information to address the uncertainties. The evaluation committee will consider this information and other stakeholder comments at a second meeting.

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 the technology 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 from the Medicines and Healthcare products Regulatory Agency was available. The committee discussion was based on the full population in the TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ trials, but subgroups effects based on apolipoprotein (APO) E4 carrier status were also considered.

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 APO E4 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 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. Alzheimer's disease can be confirmed by the presence of beta amyloid in the brain, using a positron emission tomography (PET) scan or cerebrospinal fluid test. 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 emphasised that all people with mild cognitive impairment caused by Alzheimer's disease eventually progress to having dementia. They 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 dementia, 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 anticipated licensed indication. People with mild cognitive impairment caused by Alzheimer's disease and mild dementia caused by Alzheimer's disease with confirmed amyloid pathology would be eligible to have donanemab alongside established clinical management, including existing treatments. The clinical experts advised that because the treatment window for having donanemab is more limited than existing options, 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 and includes:

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

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, including additional MRIs if needed.

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). People in the study had evidence of abnormalities in amyloid and tau proteins. This included having low-to-medium or high levels of tau protein on a PET scan. TRAILBLAZER-ALZ 2 was done in 277 sites in 8 countries including the UK. The trial randomised 1,736 people; 860 had donanemab and 876 had 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 (not stratified by tau level) as the basis for decision making. The EAG noted that the company's phase 2 trial, TRAILBLAZER-ALZ, had a similar design to TRAILBLAZER-ALZ 2 but was not included in company's 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 this was not provided. 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 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 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 decided that results from TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ would be generalisable to people who might have donanemab in NHS clinical practice. It concluded that the results of both trials are relevant to the decision problem and should be explored by the company in a meta-analysis.

Measures of cognition and function

3.6 The primary outcome of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ was change in the integrated Alzheimer Disease Rating Scale (iADRS) at 76 weeks from baseline. This 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). A key secondary outcome of the trials was change in clinical dementia rating scale sum of boxes (CDR-SB) at 76 weeks from baseline. This 5-point scale characterises cognitive and functional performance across 6 domains (memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care). The company used TRAILBLAZER-ALZ 2 CDR-SB results to inform the treatment effect of donanemab in the economic model (see section 3.11). The hazard ratio for this treatment effect was 0.62 (95% confidence interval [CI] 0.52 to 0.75). At clarification, the company provided a scenario analysis using iADRS results from TRAILBLAZER-ALZ 2 to model donanemab's treatment effect. The hazard ratio applied in this scenario analysis was 0.70 (95% CI 0.58 to 0.84). 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 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 committee agreed that both CDR-SB and iADRS measure features of cognition and function that are relevant to the decision problem. It noted that the results of both TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ are relevant to the decision problem (see section 3.5). The committee decided it was acceptable to use CDR-SB in the model. It concluded that it would like the company to explore alternative hazard ratios for disease progression for CDR-SB and iADRS, from a meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ.

Clinical-effectiveness results

3.7 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% CI) [p-value]**	**% difference**	**Least squares mean difference (95% CI) [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 submissions from the Association of British Neurologists and Faculty of Public Health stated it was unclear if the trial results were 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. The EAG advised that European consensus is that slowing of progression by 30 to 50% is clinically meaningful. The committee noted 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 EAG noted variability in the size of the treatment differences when comparing the results of the 2 key trials. The treatment difference was smaller on the iADRS and larger on the 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 test the robustness of the clinical-effectiveness results (see section 3.8). The committee acknowledged that in the trials donanemab led to less of a decline in cognition and function scores than placebo at 76 weeks. It concluded it would like to see further analysis of the clinical trial results (see sections 3.6, 3.8 and 3.9).

Risks of bias

3.8 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 amyloid-related imaging abnormalities (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 over- or under-estimated. At clarification, the company provided a sensitivity analysis of CDR-SB and iADRS outcomes. In this analysis, people were removed at their first occurrence of ARIA or infusion-related reactions if they had not already experienced disease progression. The company produced hazard ratios for disease progression with censoring for ARIA and infusion-related reactions. It stated that small changes in the hazard ratios for disease progression were seen compared with the base-case analysis. The company's results are confidential and cannot be reported here. The EAG noted these results affect its base-case incremental cost-effectiveness ratio (ICER) less for CDR-SB than for iADRS. 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. The risk-of-bias assessments 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'. The company noted that the primary efficacy analyses were based on the modified intention-to-treat (ITT) population (that is, people with a baseline and at least one post-baseline efficacy measurement based on randomised treatment). 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's results are confidential and cannot be reported here. The committee acknowledged 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 concluded that the company should explore this further through sensitivity analysis based on a meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ for CDR-SB and iADRS.

Subgroup effects by APOE4 allele status

3.9 The company considered the APOE4 allele status of trial participants. It noted that a statistical interaction test showed that being homozygous for the APOE4 allele was not a treatment-effect modifier for donanemab. The company shared treatment-effect results for donanemab from TRAILBLAZER-ALZ 2 at week 76, by APOE4 allele status (table 2).

Table 2 Treatment difference at 76 weeks for donanemab compared with placebo on iADRS and CDR-SB by APOE4 allele status

	iADRS		CDR-SB	
APOE4 allele status (copies of gene)	**Adjusted mean difference**	**% difference (95% CI)**	**Adjusted mean difference**	**% difference (95% CI)**
Non-carriers (0)	4.58	28% (12 to 44)	-0.76	29% (11 to 46)
Heterozygote (1)	2.87	24% (8 to 40)	-0.73	34% (18 to 49)
Homozygote (2)	1.01	9% (-22 to 40)	-0.41	18% (-8 to 44)

The committee noted that the confidence intervals for percentage difference between donanemab and placebo crossed zero in the homozygous for APOE4 subgroup, indicating a lack of statistically significant treatment effect in these patients. The company noted that the homozygous subgroup had a small sample size leading to uncertainty in the results. The EAG noted that 213 people were included in the homozygous subgroup for the analysis of iADRS and 220 people for CDR-SB. It asked the company whether it would be feasible to obtain a hazard ratio for progression for the homozygous subgroup of TRAILBLAZER-ALZ 2. The company stated that it was possible to calculate a hazard ratio for progression on iADRS and CDR-SB for the 3 APOE4 allele subgroups. It stated that using CDR-SB the hazard ratio for progression for the homozygous subgroup was 0.65 with wide confidence intervals. The committee acknowledged that donanemab may have a smaller treatment effect in people who are homozygous for the APOE4 allele than in people who are heterozygous for the allele or are non-carriers. It decided that it would like to explore the APOE4 allele subgroup results further, including with the option to use hazard ratios for disease progression based on the meta-analysis (see section 3.6) for the homozygous subgroup in the economic model. The committee concluded it would like to see a sensitivity analysis based on TRAILBLAZER-ALZ 2 APOE4 allele subgroup 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. 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 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 and the death state, which was absorbing. People could start donanemab in the model in the mild cognitive impairment (20.4%) or mild dementia caused by Alzheimer's disease (79.6%) health state, defined by MMSE score. People could be on or off treatment in the mild cognitive impairment, mild dementia caused by Alzheimer's disease and moderate 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 in the company's base case. This was based on NACC UDS data from Spackman et al. 2012. Clinical experts advising the EAG advised that values from the European GERAS study (Belger et al. 2019) were more suitable, including because a higher rate of residential care was estimated 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. 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 but it preferred the EAG's source for annual risk of residential care.

Mortality

3.12 In the company's model, 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 risk of death for people with mild cognitive impairment caused by Alzheimer's disease was the same as the general population or higher. The company 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 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 showed that mortality risk increases as Alzheimer's disease progresses. It also noted that this had been 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 slightly 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 for variable mortality in the mild, moderate or severe dementia caused by Alzheimer's disease health states that was 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 base case. The EAG advised the company's scenario values were not plausible because the mortality risk was higher for mild dementia caused by Alzheimer's disease (1.79) than moderate dementia caused by Alzheimer's disease (1.75). The company commented that the confidence intervals of these hazard ratios

overlapped, indicating they were not significantly different. The EAG explained that it 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, 3.1 and 6.6 for mild, moderate and severe dementia caused by Alzheimer's disease health states respectively. The EAG noted that applying these values to the company's base-case model led to a large increase in the ICER for donanemab. 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. They noted that these patients cannot communicate their needs and this makes it difficult to identify and manage concurrent illnesses such as urinary tract infections. 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 scenario values for mortality risk in mild or moderate dementia caused by Alzheimer's disease were lower than reported in all of the published sources that the EAG identified. The committee decided there is uncertainty about the risk of death across Alzheimer's disease severities. It concluded that the EAG's approach was based on recent evidence that was most closely aligned with the population modelled for donanemab. So, it preferred to use the EAG's values for decision making.

Long-term assumptions for full treatment effect

3.13 The company's model assumed 90% of people stopped donanemab after a fixed duration of 18 months. This was based on the anticipated marketing authorisation indication. 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 severe dementia caused by Alzheimer's disease health state or because an adverse event led to treatment stopping. The EAG's clinical experts noted there is limited infrastructure in place in the UK to monitor amyloid clearance by PET scan. So, the EAG assumed all people would have donanemab for up to 18 months. The committee noted that the NHS England submission estimated that 15% of people would have an amyloid-PET scan and most people would continue donanemab treatment for 18 months. 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 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 after the last donanemab dose. So, the company assumed that the full treatment effect of donanemab on and off treatment lasted 5 years in the model. The committee noted that at the time of the first committee meeting no trial evidence was available on the clinical effects 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. 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 clinical effects after treatment stops. But it thought the company had not provided evidence linking reduced amyloid levels with donanemab with clinically relevant changes in cognition and function in Alzheimer's disease. 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 treatment effect 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 lasted 2.5 years in the EAG's base case. The company commented that in the EAG's approach, all benefit of donanemab is lost when the amyloid positivity threshold is reached (24 centiloids or more) but this is about one-quarter of the level of amyloid seen at baseline in the trial (more than 100 centiloids). The EAG advised there is uncertainty in the company's estimated rate of reaccumulation. But the EAG noted that its own model also included subsequent waning (see section 3.14). The clinical experts advised there is great uncertainty about the potential long-term treatment effects of donanemab. They noted that whether the reduced decline in cognition and function seen in the trial is maintained after stopping treatment and, if so, for how long are important unanswered questions about donanemab. 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. It concluded that in the absence of

further evidence it preferred the EAG's approach, which was based on the limited clinical trial evidence presented, but would like other scenarios to be explored.

Long-term assumptions for waning

3.14 The company's model assumed that the full treatment effect of 18 months of donanemab treatment lasted 5 years (see section 3.13). After 5 years, the company assumed a period of treatment waning that lasted a further 5 years. This was modelled as a linear decline to zero. The committee noted that the company presented no trial evidence about how donanemab's treatment effect might wane after stopping. The EAG noted that this meant donanemab was assumed to have a total duration of effect (full or waned) of 10 years in the company's model, based on a maximum 18-month treatment period. The EAG preferred to assume a shorter 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 model prediction that amyloid would take 3.5 years to reaccumulate. Using the EAG's approach, donanemab was assumed to have a total duration of effect (full and waned) of 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 base-case model led to a large increase in the ICER for donanemab. 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. The committee decided that how the treatment effect of

donanemab wanes after stopping is unknown. So, the company's and EAG's modelling of long-term treatment waning is highly uncertain. The committee concluded that in the absence of further evidence it preferred the EAG's approach, which was more in line with the company's model prediction that amyloid would take 3.5 years to reaccumulate. It would also like other scenarios to be explored.

Utility values

People living with Alzheimer's disease

3.15 The company explained that no EQ-5D data were collected in the TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ trials. 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. In this 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 also 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 such 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 including because people adapt to the symptoms of their condition. So, they are not recording their quality of life relative to true full health. The committee decided, based on the evidence presented at the first committee meeting, that the EAG's preferred values are relevant UK estimates. But it concluded that it would like to see further information from the company and EAG on their approaches to utility values, which consider the concerns and the uncertainty they created. This should include further justification on the use of proxy values, with reference to the available literature.

Carers

3.16 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 that 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 large 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. So, it 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. But it noted that applying its preferred utility values to the company's base-case model led to a large increase in the ICER for donanemab. The committee noted clinical expert comments that some people living with Alzheimer's disease can be reasonably independent in the earlier stages (see section 3.12). 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 source of utility data being for the primary carer. It decided that the EAG's approach to calculating carer utilities was based on a large study giving UK relevant estimates, so appeared reasonable. The committee agreed it did not have enough information to make a decision about the company's approach to deriving carer utilities. It encouraged the company to justify and explain its approach further.

Costs

Infusion costs

3.17 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 2021/2022 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 identified a different infusion cost that it decided 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. The committee noted that the NHS England infusion cost was above £600 when uplifted to current prices. NHS England explained that its preferred cost is broadly consistent with costing of administration of a monoclonal antibody as a COVID treatment. The committee noted that cost should reflect the health system resources required for giving an infusion of donanemab. The committee noted that applying NHS England's model costs (infusion and other costs) led to a large increase in the company's and EAG's base-case ICERs (see section 3.22). The committee decided that the large difference in the infusion costs estimated by the company and NHS England had not been sufficiently explained, which led to considerable uncertainty. So, it was unable to determine a preferred cost for use in modelling. It concluded that it would like to see further information, including a breakdown of expected resource use, from the company and NHS England that fully explained the estimated costs and explored alternatives.

Outpatient consultant visits

3.18 The EAG advised the company's estimates for the diagnosis and monitoring of people with early Alzheimer's disease were broadly

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 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 informed by clinical expert advice. It decided that the cost of an outpatient consultant visit should be included for all people having APOE4 testing. It concluded that there was uncertainty about whether additional on-treatment monitoring visits should be included and this requires further clinical input, including from NHS England.

Healthcare resource use

3.19 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 EAG preferred to use these health-state costs from Wittenberg not including unpaid care costs in its base case. 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 to avoid double-counting of costs. The committee decided that it was not appropriate for the company to include unpaid care costs in its model. It concluded that it preferred the EAG's approach to costing healthcare resource use.

Cost-effectiveness estimates

Committee's preferred assumptions

3.20 The committee concluded that the cost-effectiveness estimates were very uncertain and further analyses are needed (see sections 3.6, 3.8 and 3.9). It agreed the company's overall model structure is acceptable for decision making (see section 3.11). It concluded that it could state some preferred assumptions based on the current model. That is, using the EAG's:

- source for annual risk of residential care (see section 3.11)
- values for mortality, which included an assumption that risk of death increases as Alzheimer's disease becomes more severe (see section 3.12)
- long-term treatment-effect assumptions (see sections 3.13 and 3.14), but the committee also asked for other scenarios to be explored
- preferred values for patients and carer utilities (see sections 3.15 and 3.16), based on the evidence presented at the first meeting. But the committee asked for further justification of both the EAG and company approach

- assumption that for all people having an APEO4 test, the costs should include both the test and an outpatient consultant visit (see section 3.18)
- approach that removed unpaid care costs and a one-off end of life care cost from the modelled healthcare resource use (see section 3.19).

Uncertainty in the cost-effectiveness estimates

3.21 The committee acknowledged the 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 3.6, 3.8, 3.9 and 3.10)
- mortality risk that should be assumed in different Alzheimer's disease severities (see section 3.12)
- proportion of people (if any) who would stop donanemab before 18 months based on amyloid-PET scan results (see section 3.13)
- long-term treatment assumptions, noting it is highly uncertain if and for how long the full treatment effect of donanemab is maintained then wanes after stopping (see sections 3.13 and 3.14)
- utility values used in the model (see sections 3.15 and 3.16)
- costs including infusion cost and whether additional on-treatment monitoring visits should be added to the model (see sections 3.17 and 3.18).

The committee advised it would like to see the following analyses and further evidence to enable it to decide on the cost effectiveness of donanemab:

- the iADRS and CDR-SB treatment effects when the results from TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ are combined in a meta-analysis (see section 3.6). This should include:
  - mean change and treatment-difference results for the 2 analysis methods used (natural cubic spline with 2 degrees of freedom model and mixed model for repeated measures) with alternative hazard ratios generated and the option to apply these in the model
  - sensitivity analysis for the occurrence of ARIA events or infusion-related reactions (see section 3.8)
  - mean change and treatment difference results for subgroups based on APOE4 allele status (see section 3.9) with alternative hazard ratios generated and the option to apply these in the model
  - sensitivity analysis of treatment effects for subgroups based on APOE4 allele using TRAILBLAZER-ALZ 2 only
- 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 (see section 3.13)
- justification for the proposed link between the amyloid-reducing effects of donanemab and clinically relevant changes in cognition and function in Alzheimer's disease that informed the company and EAG's long-term treatment assumptions (see sections 3.13 and 3.14)
- considerations of proxy utility values and adaptation by people living with Alzheimer's disease (see section 3.15)
- further information from the company about its vignette studies and further justification for using this approach for carer utilities (see section 3.16)
- further information from the company and NHS England that fully explains estimated infusion costs and explores alternatives (see section 3.17) and consideration of whether additional on-treatment monitoring visits should be added to the model (see section 3.18)

- disaggregated, discounted and undiscounted results for the company's and EAG's base cases by modelled health states, including average occupancy, time spent, utilities and costs (see section 3.11).

Company and EAG cost-effectiveness estimates

3.22 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 first committee meeting included a confidential discounted price for donanemab. The committee noted that the cost-effectiveness estimates were highly uncertain (see section 3.21). The company's deterministic base-case ICER for donanemab compared with placebo was about £20,000 per QALY. The EAG's base-case ICER was about £150,000 per QALY, which is considerably above the range normally considered cost effective for routine NHS use. Applying NHS England's model costs (infusion and other costs) to the EAG's base case increased the ICER further to about £180,000 per QALY. The committee concluded that it could not recommend donanemab for routine use. This was because the most plausible ICER was likely considerably above the range normally considered cost effective, and because of uncertainty in all the cost-effectiveness estimates.

Managed access

3.23 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 company proposed that data could be collected from the extension phases of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. It explained that other trials of donanemab are ongoing or planned. These include the TRAILBLAZER-REAL US and other studies outside the US with long-term follow up that aims to address

clinical uncertainty. The company also proposed collecting real-world evidence on diagnosis, disease management and costs. The clinical lead for the Innovative Medicines Fund highlighted that the usefulness of data from the trial's extension phases in resolving key uncertainties would be limited by their duration. They noted it was unclear how many people would be followed to the end of the longer-term studies. They advised that some uncertainties may not be addressed by further data collection. 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 it was unclear whether data collection proposed by the company would sufficiently address the key uncertainties. It noted that no NHS-level data collection was proposed, so the most feasible way to gather further data would be through trials. The committee decided that based on the range of cost-effectiveness estimates presented it was unlikely that donanemab had the plausible potential to be cost effective. So, the committee concluded that donanemab did not meet the criteria to be considered for a recommendation with managed access. But it would welcome an updated managed access proposal from the company. This should include further information on how it would address the key uncertainties the committee identified and present plausibly cost-effective ICERs.

Other factors

Equality and health inequality issues

3.24 Submissions from the clinical and patient experts identified potential equality and health inequality concerns for consideration. These were:

- inequality in getting an Alzheimer's disease diagnosis and accessing care. This will be exacerbated by introducing the complex diagnostic pathway for donanemab. People without a carer who can help them get a timely diagnosis will 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 may increase because existing services that are already under strain would be delivering the treatment. The effect of this is likely to be seen more profoundly 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

3.25 Stakeholder submissions throughout the appraisal 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

- 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 3.22):
  - 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 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 3.21). So, the committee was unable to reach a conclusion on the effects of uncaptured benefits and costs.

Conclusion

Recommendation

3.26 The committee acknowledged the high uncertainty associated with the modelling, including in the long-term evidence for donanemab. It decided that more evidence was needed to generate robust cost-effectiveness estimates. It noted that the EAG's and company's base cases were associated with uncertainty, and the most plausible cost-effectiveness estimates were above the range normally considered a cost-effective use of NHS resources. So, it did not recommend donanemab for treating mild cognitive impairment or mild dementia due to Alzheimer's disease in adults who are APOE4 heterozygotes or non-carriers, either for routine NHS use or with managed access.

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

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 and a project manager.

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