NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Lecanemab 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 lecanemab 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).

For this evaluation, stakeholders have previously been consulted on the draft guidance, including the summaries of the clinical and cost effectiveness, the recommendations for lecanemab and equalities issues.

Following 2 upheld appeal points, the appeal panel remitted the final draft guidance to the committee. For this consultation, stakeholders are requested to specifically consult on section 3.20 of the final draft guidance and respond to:

- NHS England's Infusion Cost Estimates Document.

Issue date: March 2026

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using lecanemab in the NHS in England.

For further details, see NICE technology appraisal and highly specialised technologies guidance: the manual.

The key dates for this evaluation are:

- Closing date for comments: 28 April 2026
- Second evaluation committee meeting: 10 June 2026
- Details of the evaluation committee are given in section X

1 Recommendations

1.1 Lecanemab is not recommended, within its marketing authorisation, for treating mild cognitive impairment and mild dementia caused by Alzheimer's disease in adults who are heterozygous for apolipoprotein E4 or do not have the gene.

1.2 This recommendation is not intended to affect treatment with lecanemab 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.

What this means in practice

Lecanemab is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that lecanemab is value for money in this population.

Why the committee made these recommendations

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

Evidence from a clinical trial suggests that people having lecanemab continue to have worsening cognitive function over time. But this is at a slower rate than in people having placebo (both added to usual treatment). There is a lack of evidence on the long-term effects.

There is a high level of uncertainty in the economic model. Also, the most plausible cost-effectiveness estimate for lecanemab is much higher than what NICE considers an acceptable use of NHS resources. This is because:

- the benefit it provides is relatively small, but
- the cost for providing it is high (including fortnightly infusions in hospital and intensive monitoring for side effects). So, lecanemab is not recommended for routine use.

Because lecanemab is not cost effective and because of uncertainties that would not be addressed in a period of managed access, it is not recommended with managed access.

2 Information about lecanemab

Marketing authorisation indication

2.1 Lecanemab (Leqembi, Eisai) is indicated 'for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein Eε 4 (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 lecanemab.

Price

2.3 The list price of lecanemab is £275 for 200 mg solution for infusion and £545 for 500 mg solution or infusion (excluding VAT; company submission).

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

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published at Eisai: Sustainability (webpage).

3 Committee discussion

The evaluation committee considered evidence submitted by Eisai, 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 lecanemab from the Medicines and Healthcare products Regulatory Agency was available. The committee discussion was based on the full population in the Clarity AD trial, but subgroup analysis based on apolipoprotein (APO) E4 carrier status was also considered. During the second and third committee meetings, the committee discussion was based on the marketing authorisation indication population. This population only includes people with mild cognitive impairment (MCI) and mild dementia caused by Alzheimer's disease who are heterozygous for APOE4 or do not have the gene.

The condition

Alzheimer's disease

3.1 Alzheimer's disease is a progressive neurological condition, and is estimated to be the most common type of dementia. Research suggests that it affects about 6 in 10 people with dementia, although this estimate is uncertain. Alzheimer's disease is also the leading cause of death in the UK. It 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 neurone function. The major risk factor for dementia is age. More than 95% of people affected are over 65 years. The APOE4 gene is associated with an increased risk of developing Alzheimer's disease. 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. 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. The patient expert statements described the loss of independence and confidence after a diagnosis of Alzheimer's disease, and the hope that a first potential disease-modifying treatment would bring. The patient experts also identified the significant role of carers in looking after people with Alzheimer's disease, and the life-changing effects of the condition on them. Statements from carers of people with the condition 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 added that the underlying pathology starts at least 10 years before symptoms present. The committee recalled the first-hand experiences shared by people with Alzheimer's disease. It concluded that the condition is progressive and 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 MCI 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 MCI caused by Alzheimer's disease, which refers to the set of symptoms that occur before the dementia stage of the condition. Guidelines from the National Institute on Aging and the Alzheimer's Association in the US define the MCI stage as mild changes in memory and thinking that are noticeable and measurable, and 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. If the diagnosis is uncertain and Alzheimer's disease is suspected, NICE's guideline on dementia recommends considering a positron emission tomography (PET) scan or cerebrospinal fluid (CSF) test to check for presence of amyloid beta. The number of people diagnosed with mild dementia because of Alzheimer's disease at any one time in England is about 80,000. More than a third of people with all types of dementia in England do not have a dementia diagnosis. The number of people with MCI 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 noted that people with MCI caused by Alzheimer's disease will eventually progress to having dementia. But they highlighted that MCI caused by Alzheimer's disease is rarely diagnosed in the UK.

In response to the draft guidance, the UK Faculty of Public Health noted that there is no consensus that having a positive amyloid beta test always leads to Alzheimer's disease. It noted that the 'amyloid hypothesis' states that people have Alzheimer's disease if they have a positive amyloid beta test. This is regardless of the presence or absence of Alzheimer's symptoms. But, under this hypothesis, many people are labelled as having Alzheimer's disease despite not having dementia and never developing dementia over their lifetime. It explained that the National Institute of Aging recently withdrew its endorsement of this amyloid hypothesis. The clinical experts also noted that most people with MCI do not have a confirmed diagnosis, and that there are no standardised measures to clearly separate the disease stages. They explained that some people diagnosed with MCI caused by Alzheimer's disease in the NHS are followed up. But many people are discharged from memory clinics back to primary care, with the advice to be rereferred once symptoms progress. The company cited research showing that about 90% of people with dementia would want to have an accurate diagnosis, even

if there were no treatments available. The committee noted that there are challenges with diagnosing MCI 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 MCI caused by Alzheimer's disease. For later stages of the 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, when there is an intolerance or contraindication to acetylcholinesterase inhibitors
  - severe Alzheimer's disease.

For people with an established diagnosis of Alzheimer's disease already on an acetylcholinesterase inhibitor, the NICE guideline recommends adding memantine as an option for moderate and severe disease.

The clinical experts explained that current treatments for Alzheimer's disease have symptomatic benefits for some people. But none of the options available are disease modifying. The committee concluded that current treatment options are limited for mild dementia caused by Alzheimer's disease. It also concluded that there is a significant unmet need for treatment options to prevent or delay progression from MCI to mild dementia caused by Alzheimer's disease.

Treatment positioning of lecanemab

3.4 The patient, clinical and commissioning experts highlighted that using lecanemab (and other disease-modifying treatments) in the NHS would need significant changes to the existing diagnostic pathway (see section 3.2). The committee papers in the submission from NHS England include an outline of the new diagnostic pathway. The changes recommended include:

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

NHS England also noted that introducing disease-modifying treatments would substantially increase demand on primary care and memory clinics because of increased awareness of MCI and availability of treatment options. The committee heard that a blood test for amyloid beta was being developed, but was not available at the time of the meeting. If lecanemab were to be recommended, people with MCI or mild dementia caused by Alzheimer's disease with confirmed amyloid pathology and who are heterozygous for APOE4 or do not have the gene would be eligible to have lecanemab alongside established clinical management (including existing treatments). The summary of product characteristics for lecanemab notes that it can cause amyloid-related imaging abnormalities-oedema (ARIA-E) and -haemosiderin deposition (ARIA-H). So, an MRI should be available during the lecanemab treatment period. Commissioning experts identified that the treatment pathway for lecanemab would be more complex than for current treatments, and would include:

- 2-weekly intravenous infusions of lecanemab in secondary care
- routine outpatient follow-up appointments every 3 months, in memory clinics

- routine MRIs before starting treatment, and before the fifth, seventh and 14th infusions
- acute management of amyloid-related imaging abnormalities (adverse events associated with lecanemab treatment), including additional MRIs (if needed).

The committee concluded that if lecanemab were recommended, the NHS would need to significantly change the current diagnostic and treatment pathways in Alzheimer's disease.

Clinical effectiveness

Clarity AD trial

3.5 The main source of clinical-effectiveness evidence for lecanemab was the Clarity AD trial. This was a phase 3, randomised, placebo-controlled, superiority double-blind trial. It investigated the efficacy of lecanemab compared with placebo in people 50 to 90 years with early Alzheimer's disease dementia. The trial recruited 1,795 people. A total of 1,486 completed the 18-month study and, of these, 729 were randomised to lecanemab and 757 were randomised to placebo. The mean age was 71 years and 52% of people in the trial were women. The trial was carried out in 235 sites around the world, including 8 sites in the UK. The primary outcome was change in clinical dementia rating scale sum of boxes (CDR-SB) at 18 months 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).

At 18 months, people in the lecanemab arm had an adjusted mean change in CDR-SB of 1.213 compared with 1.663 for placebo. This resulted in an adjusted mean difference between arms of -0.451 (-27.1%, p=0.00005) in the intention-to-treat full analysis set. The company explained that this meant lecanemab reduced the decline in CDR-SB by

27% at 18 months. The committee questioned the appropriateness of assuming that missing values in the trial were missing at random. The company explained that it explored this assumption in sensitivity analyses, including assuming that people who were missing to follow up progressed to moderate Alzheimer's disease. It noted that varying this assumption had only a very small impact on the cost-effectiveness results.

At the second committee meeting, the company shared clinical-effectiveness results for the population indicated in the marketing authorisation (so excluded people who were APOE4 homozygotes). At 18 months, the results for people in the lecanemab arm adjusted to exclude APOE4 homozygotes were:

- a mean change in CDR-SB of 1.151 compared with 1.730 for placebo, resulting in a mean difference between arms of -0.579 (-33.5%, $p<0.00001$)
- a mean difference in Alzheimer's Disease Assessment Scale-Cognitive subscale 14 (ADAS-Cog14) of -1.633, equivalent to 28% less decline ($p<0.001$)
- a mean difference in Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment (ADCS MCI-ADL) of 2.234, equivalent to 39% less decline ($p<0.0001$).

The most common adverse reactions in Clarity AD (excluding APOE4 homozygotes) were infusion-related reactions, ARIA-H, falls, headache and ARIA-E. The company also shared the results from other secondary and health-related quality-of-life outcomes in Clarity AD. But the company considers these results confidential, so they are not reported here. The committee concluded that Clarity AD was relevant for the decision problem and for investigating lecanemab for treating MCI or mild dementia caused by Alzheimer's disease.

Clinically meaningful treatment effect

3.6 The EAG and the submission from the Faculty of Public Health questioned whether the treatment effect of lecanemab was clinically meaningful. The Faculty of Public Health submission explained that literature suggests a minimum clinically important CDR-SB difference is 0.98 for MCI and 1.63 for mild dementia caused by Alzheimer's disease. The treatment effect seen with lecanemab in Clarity AD was smaller than both of these values. It also noted that the observed treatment effect for lecanemab at 18 months was about half of the treatment effect that is seen with current treatments at 6 months. But the patient and clinical experts explained that it was inappropriate to compare the treatment effect of lecanemab with that of the acetylcholinesterase inhibitors and memantine. This was because they noted that lecanemab is disease modifying and has a different mechanism of action from these treatments. The submissions from the Royal College of Psychiatrists and Association of British Neurologists said that the observed treatment effect of lecanemab in Clarity AD was clinically meaningful. It noted that it equated to a slowing in disease progression of between 4 and 6 months. Clinical experts consulted by the EAG also identified that a difference in CDR-SB of 0.451 would be seen as a clinically meaningful change by people with Alzheimer's disease. The company said that lecanemab is a disease-modifying treatment, so the full long-term benefits of lecanemab may not be apparent at 18 months. It showed evidence that, at 24 months, people who had started Clarity AD on lecanemab had a 16% slower decline in CDR-SB than people who switched from placebo to lecanemab after the trial at 18 months. The committee noted that there were different rates of attrition between the 2 groups, which may have contributed to some of the observed differences. It also noted that the observed treatment effect of 0.451 was the average effect across the full intention-to-treat population in the trial. The patient and clinical experts noted that Alzheimer's disease is a highly heterogeneous disease. So, some people may experience a clinically meaningful slowing of disease progression when having lecanemab, but others may not. They added that a larger treatment effect

may also be seen at earlier disease stages. The clinical experts noted that CDR-SB is commonly used as an outcome measure for moderate to severe Alzheimer's disease. But they explained that it is not very sensitive in detecting changes in early Alzheimer's disease, particularly for people with MCI. The committee noted that 1 increment on the CDR-SB scale is 0.5. The clinical experts added that a 0.5 change in CDR-SB can mean a change from benign forgetfulness to losing daily independence for some people. So, they said that a 0.5 change in CDR-SB can be clinically meaningful, particularly for younger people or people with fewer comorbidities. The patient and clinical experts agreed that a 6-month delay in disease progression was a clinically meaningful difference. They thought that a 4- or 5-month difference was also likely to be meaningful. The patient experts added that any slowing of disease worsening would be meaningful because it would mean more time socialising, driving and being independent.

At the second committee meeting, the committee considered the clinical-effectiveness results for the population included in the marketing authorisation (MCI and mild dementia caused by Alzheimer's disease in adults who are heterozygous for APOE4 or do not have the gene). The adjusted mean difference in CDR-SB was -0.579 between lecanemab and placebo (see section 3.5). The committee noted that the treatment effect of lecanemab compared with placebo was larger in the population included in the marketing authorisation than in the full population that was included in Clarity AD. The company shared a breakdown of CDR-SB changes by threshold CDR-SB score and CDR-SB domain. The results are commercial in confidence and cannot be reported here. The EAG noted that the results supported a treatment effect of lecanemab across CDR-SB domains and levels of cognitive or functional worsening. But it noted some variation in the size of the observed effect. The committee concluded that lecanemab had a clinically significant treatment effect. But it noted that the treatment effect was small and that the duration of

treatment effect was uncertain. It also noted that the CDR-SB lacks sensitivity to detect disease changes for people with MCI.

Standard care in the trial

3.7 The EAG noted that treatments used alongside lecanemab in Clarity AD were different to those specified in the decision problem and the EAG's clinical expert opinion of NHS clinical practice. The clinical experts at the committee meeting agreed that the concomitant treatments used in Clarity AD were different to NHS clinical practice. The decision problem identified that non-pharmacological treatments are used for people with MCI caused by Alzheimer's disease, and acetylcholinesterase inhibitors are used for people with mild dementia caused by Alzheimer's disease. The EAG's clinical expert largely agreed, estimating that:

- For people with MCI caused by Alzheimer's disease, a minority have off-label acetylcholinesterase inhibitors and almost none have memantine.
- For people with mild dementia caused by Alzheimer's disease, 70% have acetylcholinesterase inhibitors and 5% have off-label memantine.

The company shared the proportion of people in Clarity AD who had concomitant treatment with acetylcholinesterase inhibitors and memantine. The figures are confidential and cannot be reported here. But the company argued that the figures largely aligned with real-world use figures in Europe from reported that:

- For people with MCI caused by Alzheimer's disease, 31% had acetylcholinesterase inhibitors and 8% had memantine.
- For people with mild dementia caused by Alzheimer's disease, 89% had acetylcholinesterase inhibitors and 7% to 21% had memantine.

At the EAG's request, the company shared CDR-SB results from Clarity AD for people with MCI excluding people who had an

acetylcholinesterase inhibitor or memantine. It also shared results for people with mild dementia excluding people who had memantine. The results are confidential and cannot be reported here. The EAG noted that the treatment effect of lecanemab was reduced when people who had acetylcholinesterase inhibitors or memantine were excluded from the analysis. But the EAG noted that these results should be interpreted with caution because of the small sample size. The clinical experts explained that lecanemab is used alongside current treatments and its mechanism of action is different from other treatments. So, they would not expect the use of other treatments to significantly change the treatment effect of lecanemab. The committee recalled that people with MCI caused by Alzheimer's disease have no current treatment options. But people with mild dementia caused by Alzheimer's disease can have an acetylcholinesterase inhibitor (see section 3.3). It noted that the treatments used as standard care in Clarity AD differed from what is used in NHS clinical practice. The committee concluded that it was acceptable to use the Clarity AD trial population for decision making. But it acknowledged that the differences in the treatments used in Clarity AD compared with NHS clinical practice increased the uncertainty.

Trial population generalisability

3.8 The EAG questioned the generalisability of Clarity AD to NHS clinical practice. The clinical expert consulted by the EAG noted that the proportion of people with MCI and mild dementia caused by Alzheimer's disease in the UK is likely different to that reported in Clarity AD. The trial reported that 62% of people in the intention-to-treat population had MCI and 38% had mild dementia. But a clinical expert consulted by the EAG expected that 38% of people would have MCI and 62% would have mild dementia. The expert also noted that the primary outcome of CDR-SB is not used in UK clinical practice. Submissions from the Faculty of Public Health questioned whether functional unblinding might be a concern because of very different rates of infusion reactions for lecanemab

(26.4%) and placebo (7.4%). This means that people in the trial may have been able to guess whether they were having lecanemab or placebo. Some of the outcome measures in the clinical trial were informed by patient or carer judgements, so this could have biased the results. The submissions also noted that baseline characteristics and the way people were diagnosed in the trial were different to the UK. The company noted that the baseline characteristics of people in Clarity AD were thought to be generalisable to the UK by the clinical experts it consulted. But, in response to the draft guidance, the Faculty of Public Health did not agree. It noted the difference in average age from Clarity AD (71 years) and a recent UK real-world study (Cognitive Function and Ageing Study 2, 83 years). It also noted that only 8% of a US-based sample of people with early Alzheimer's disease would be eligible for Clarity AD.

During the committee meeting, the clinical experts highlighted that MCI caused by Alzheimer's disease is rarely diagnosed in the UK (see section 3.2), so the number of people with this condition is not known. They added that the number of people diagnosed with MCI would likely increase if lecanemab were recommended. The clinical experts explained that, although CDR-SB is not used in UK clinical practice, there is no consensus on what measure should be used. They added that they would expect the observed treatment effect of lecanemab to be realised in UK clinical practice. The committee considered whether Clarity AD was generalisable to UK clinical practice. It recalled its conclusion on the generalisability of the trial comparators (see section 3.7). It noted that the proportion of people with MCI and mild dementia caused by Alzheimer's disease in the UK is uncertain and expected to change (see section 3.11). This is because new treatment options may be approved and new diagnostic pathways and access to new medicines may be implemented. The committee noted that there were differences between the population included in Clarity AD and the population that would be eligible for lecanemab in NHS clinical practice. The committee thought that this was a

source of uncertainty, but that it was appropriate to use the results of Clarity AD in the model.

Treatment effects for subgroups

3.9 At the first committee meeting, the company shared treatment-effectiveness results for lecanemab compared with placebo from Clarity AD, split by subgroups for APOE4 carrier status and age. At the second and third committee meetings, the committee did not consider the results for APOE4 homozygotes because this group is excluded from the marketing authorisation. The adjusted mean differences in CDR-SB by APOE4 carrier status between lecanemab and placebo groups were:

- no APOE4 gene: -0.75 (41% slowing of decline)
- heterozygous, 1 copy of the gene: -0.50 (30% slowing of decline)
- homozygous, 2 copies of the gene: 0.28 (22% faster decline, confidence interval crosses zero).

The adjusted mean differences in CDR-SB for the full population included in Clarity AD, by age at baseline, were:

- 75 years and over: -0.72 (40% slowing of decline)
- 65 to 74 years: -0.37 (23% slowing of decline)
- under 65 years: -0.08 (6% slowing of decline, confidence interval crosses zero).

The committee questioned whether the larger estimated treatment effect for people over 75 years was consistent with expert opinion that people in earlier disease stages may have a larger treatment effect (see section 3.6). The company explained that the results should be interpreted with caution because of small patient numbers in each subgroup. The clinical experts explained that the result might be because there is a larger proportion of people who are homozygous or heterozygous for APOE4 in the younger age categories. The clinical

experts noted that this is expected because being homozygous or heterozygous for APOE4 increases the risk of having Alzheimer's disease at a younger age. The committee noted that age was not a stratification variable in the trial, meaning that there could have been imbalances in effect modifiers in the subgroups by age. The company gave additional detailed subgroup results at the second committee meeting, alongside further explanations that are confidential and cannot be reported here. The committee concluded that it was unable to draw meaningful conclusions from the subgroup results by age. This was because of the lack of statistical significance, and small sample sizes. The committee noted that because age is a protected characteristic, it would need to be very certain that any recommendations based on age were appropriate. Because of the limitations of the subgroup analyses, and because the experts had outlined that lecanemab leads to clinical benefit for people of all ages, it concluded that it did not have this certainty.

Economic model

Company's model

3.10 The company developed a Markov model with 5 mutually exclusive health states to estimate the cost effectiveness of lecanemab compared with placebo. The states were MCI 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. People were modelled to move between all health states besides the death state, which was absorbing. The model had a monthly cycle length and a lifetime time horizon. Health-state membership of people in the model was derived using cohort simulation in discrete time. Two separate but identical health-state structures were used for people in the community setting and people in residential care. People were modelled to start in the community setting and could then move to residential care, but could not move back to community care once in residential care. The

model included acquisition, administration, monitoring, diagnostic testing, symptomatic treatment, adverse event (ARIA-E, ARIA-H and infusion reactions), and direct medical and non-medical care costs. The committee considered whether it would be preferable for the company to have developed a patient-level simulation model. It noted that such an approach may have better reflected the potential impact of patient heterogeneity on the treatment effect. But the committee thought that the extent to which this is important for cost-effectiveness results was not clear. The committee concluded that the company's model structure reflected health states relevant to the decision problem and natural history of Alzheimer's disease. It concluded that the model structure was acceptable for decision making, taking into account the uncertainty related to the impact of patient heterogeneity.

Starting proportions in the model

3.11 At the first committee meeting, the proportion of people starting in the company's model with MCI or mild dementia caused by Alzheimer's disease was aligned with Clarity AD. But the EAG disagreed, and instead used proportions estimated by a clinical expert (see section 3.8). The committee noted that it would like to see estimates from clinical experts on what the introduction of lecanemab would do to the number of people diagnosed with MCI or mild dementia caused by Alzheimer's disease. For the second committee meeting, the company consulted 3 clinical experts. All experts expected that the proportion of people with MCI would increase over time because of knowledge of and access to treatments. One clinical expert said that the initial proportion would reflect the EAG's base case. So, the company updated its base case to align with the EAG's base case. At the third committee meeting, the company changed the proportion of people with MCI and mild dementia in its model. It changed the proportions to 20.4% with MCI and 79.6% with mild Alzheimer's disease, which were the starting proportions of the overall population of the TRAILBLAZER-ALZ 2 trial. This was to align with committee preferences at the second committee meeting for NICE's

evaluation of donanemab for treating MCI or mild dementia caused by Alzheimer's disease. The EAG agreed with this change and adopted it in its base case. The committee noted that normally it would prefer for the baseline characteristics used in the model to align with the source of efficacy data used (that is, Clarity AD). But it noted that there were differences between the population included in Clarity AD and the population that would be eligible for lecanemab in NHS clinical practice. It also noted that the proportion of people with MCI and mild dementia caused by Alzheimer's disease in the UK is uncertain and likely to change. Also, the proportion of people with MCI and mild dementia in TRAILBLAZER-ALZ 2 was more aligned to expectations in UK clinical practice. So, the committee noted that the baseline proportions were uncertain. It concluded that it would normally have preferred to use the baseline characteristics from Clarity AD. But these did not align with clinical expert opinion of NHS clinical practice. So, it concluded that it was appropriate to use the baseline proportions of MCI and mild dementia from TRAILBLAZER-ALZ 2 in this case.

Transitions to better health states

3.12 The company's model assumed that most people progressed to worse health states over time. But it allowed a proportion of the cohort to transition to better health states. For example, transition from the mild dementia health state to the MCI health state was possible. The EAG questioned the clinical validity of this assumption because the clinical experts said that Alzheimer's disease is a progressive disease. Also, lecanemab slows or delays progression to more severe health states, rather than reversing progression. The EAG shared a scenario analysis that removed transitions to better health states (that is, removed a person's ability to have temporary improvements in their Alzheimer's disease). This substantially increased the incremental cost-effectiveness ratio (ICER). The company explained that its approach was consistent with observed trial data, literature and expert opinion. It also noted that temporary improvements in the condition were seen in patient-level

longitudinal data from the National Alzheimer's Coordinating Center (NACC, see section 3.13). It added that the model had a short monthly cycle length, and movements to improved health states were temporary. It emphasised that the proportion of people who moved from worse to better health states was very small, and the time spent in the better health state was short. The clinical experts explained that it was possible for rare and short periods of improvement to occur. But overall people with Alzheimer's disease will progress to more severe disease over time. The committee noted that Alzheimer's disease is progressive. It thought that the observed changes may be because of measurement variability in clinician-reported CDR-SB or variability in a person's condition, rather than an improvement in the condition. It noted that including backward transitions was less important than accurate health-state occupancy generated in the model when compared with the trial. The committee concluded that the company's approach to modelling, in which some people had temporary improvements in their disease, was appropriate. It noted that the overall direction for people with Alzheimer's disease was disease progression, and that modelled outcomes were consistent with the trial.

Constant transition probabilities

3.13 At the first committee meeting, the company in its model assumed that transition probabilities were constant (did not change over time) for the time horizon of the model. For the first 18 months, it used transition probabilities estimated from Clarity AD data for both lecanemab and placebo. After 18 months, it based transition probabilities on Potashman et al. (2021) for placebo. This study used NACC data to estimate progression rates for people with confirmed amyloid at different stages of Alzheimer's disease. The EAG questioned the validity of the company's original approach because the Clarity AD data showed increases in people moving between health states over time. Increases over time would not be captured with constant transition probabilities. At the second committee meeting, the company changed its base case to use a multistate survival analysis to estimate transition probabilities that

changed over time for the first 18 months in the model. It took this approach because smoothed hazard plots for the indicated population showed evidence of hazards changing over time. The model included a Weibull distribution for transitions from MCI to mild dementia, from mild to moderate dementia and from mild dementia to MCI. It included an exponential distribution for transitions from moderate to mild dementia. The EAG noted that the updated approach from the company was appropriate, but it had concerns with the face validity of the modelled outcomes (see section 3.14). The committee concluded that the company's updated approach to include transition probabilities that changed over time was appropriate.

Face validity of modelled survival benefits

3.14 At the first committee meeting, the EAG thought that the company's modelling approach overestimated the benefits of lecanemab. The EAG explained that about half of the modelled quality-adjusted life year (QALY) gain in the company's base case was because of survival gains. The clinical experts explained that a survival benefit with lecanemab was plausible because mortality increases as dementia progresses. So, lecanemab could increase survival if people spent more time in the MCI health state before progressing to dementia. But the clinical experts noted that it was not possible to quantify the size of any survival benefit. The committee concluded that it would like to see transition probabilities that led to outcomes and mortality benefit consistent with trial data and clinical expectations. At the second committee meeting, the company provided an updated model to address the committee's and EAG's concerns about the face validity of the model outcomes. Among other changes, it used the mortality ratio for people with MCI compared with the general population (0.63) from Crowell et al. (2023) to estimate MCI mortality in the model. The EAG assumed that mortality for people with MCI would be the same as for people without Alzheimer's disease. This was instead of using the figure from Crowell et al. used by the company. The committee concluded that it was appropriate to use general population mortality for MCI, as in

the EAG's base case. This was because the clinical experts explained that people eligible for treatment will mostly be asymptomatic and not be considered frail (see section 3.20). At the third committee meeting, the company adopted the committee preference for using general population mortality for MCI in its base case.

Progression from mild to severe Alzheimer's disease

3.15 At the second committee meeting, the company shared information comparing health-state occupancy from the updated economic model and Clarity AD data. The figures are commercial in confidence and cannot be reported here. But the company explained that the differences in health-state occupancy were small and that the model and the trial aligned. The EAG disagreed that the latest company model accurately predicted health-state occupancy. It noted that the model underestimated occupancy of MCI and mild dementia states and overestimated occupancy of moderate dementia, severe dementia and death states compared with the trial. It thought that this could have biased the results in favour of lecanemab. The EAG's updated base case assumed that having lecanemab would not affect the proportion of people who moved directly from mild dementia to severe dementia compared with standard care. The committee noted that it was uncertain whether having lecanemab would affect the proportion of people who moved directly from mild dementia to severe dementia. It noted that:

- The ICER increased if it was assumed that treatment with lecanemab did not have any impact on moving from mild to severe dementia.
- Both the company's and EAG's ICER estimates at the second committee meeting were higher than NICE considers a cost-effective use of NHS resources, regardless of the progression assumption used.

The committee thought that the company's updated model more accurately estimated health-state occupancy compared with Clarity AD data than the model at the first committee meeting. It thought that the

updated model was suitable for decision making but still associated with substantial uncertainty.

At the third committee meeting, the company maintained its previous base case and explained that disabling the time-to-worsening hazard ratio for mild to severe dementia (as in the EAG's base case) was inappropriate. It explained that doing so decreased the overall treatment effect of lecanemab to below the efficacy observed in Clarity AD. It also shared a confidential difference in the number of people that transitioned from mild to severe Alzheimer's disease in the lecanemab and placebo arms in the trial. The EAG maintained its base case, which assumed that having lecanemab would not affect the proportion of people who moved directly from mild dementia to severe dementia compared with standard care. It explained there was no evidence of a significant treatment effect in transitions from mild to severe dementia. It reiterated that the company's model underestimated the relative state occupancy in severe dementia of lecanemab versus placebo when compared with observed state occupancy in Clarity AD. The committee concluded that, given the additional information shared by the company, there was not a clear significant treatment effect in transitions from mild to severe dementia for lecanemab. So, it concluded that assuming lecanemab would not affect the proportion of people who moved directly from mild dementia to severe dementia compared with standard care was appropriate for decision making. The committee considered whether this conclusion was consistent with its conclusions for the evaluation of donanemab for treating MCI or mild dementia caused by Alzheimer's disease. It thought that the way transition probabilities were modelled in the donanemab evaluation did not result in the same concern about the alignment between state occupancy and the trial data. Also, it noted that there were differences in the evidence bases and trial designs for donanemab and lecanemab, particularly around the timing and reason

of treatment discontinuation. So, the committee concluded that it was appropriate to apply different assumptions about progression from mild to severe dementia for the lecanemab and donanemab evaluations.

Stopping rule on entering residential care

3.16 Clarity AD did not include a treatment stopping rule for lecanemab. This meant that lecanemab was not stopped when a person's Alzheimer's disease progressed to moderate dementia. People continued lecanemab for the full 18-month trial duration unless they stopped treatment because of adverse events, loss to follow up, personal choice, withdrawal of consent, or other reasons. But the company's base case included 2 stopping rules for lecanemab (see section 3.17). The first assumed that people stopped treatment once they enter residential care. The company explained that this stopping rule was based on feedback from UK clinical experts. The clinical experts in the committee meeting explained that some people move to residential care because of disease progression. But some people move to residential care for different reasons, such as their carers' capacity. So, the clinical experts did not think it would be reasonable to apply a stopping rule based on entry to residential care in clinical practice. To account for people entering residential care not for disease progression, the company included a scenario analysis in which 10% of people in residential care continued lecanemab treatment. The committee noted that applying a stopping rule based on entry to residential care could have led to increasing health inequalities. This is because there is inequitable access to residential care. So, the committee concluded that it was not appropriate to apply a stopping rule based on entry to residential care.

At the third committee meeting, the company explained that the residential care stopping rule reflects what will happen in clinical practice, and is not a formal stopping rule. It quoted 2 experts who said that continuing treatment in residential care 'would not be appropriate' and 'bad practice'. Experts also estimated that the number of people entering residential care

permanently with mild Alzheimer's disease would be small (around 5% to 10%). The company explained that the model estimated a similar proportion of people entering residential care. It also highlighted that the rate of admissions into residential care it used did not include temporary admissions for respite care, only permanent admissions. The EAG noted that the details of the expert validation done by the company were not provided. It questioned whether the experts knew the intended context of people with mild Alzheimer's disease moving to residential care permanently. So, the EAG removed the stopping rule in its base case but assumed that only 50% of people continue treatment when entering residential care. This was to reflect the logistical challenges of the treatment setting. The committee considered that it had not heard any new evidence to change its conclusion from the second committee meeting. It understood the view of some experts that treatment would not continue in residential care. But it recalled expert testimony from previous committee meetings that they would not want to apply a stopping rule based on entry to residential care in clinical practice. Combined with the committee's concerns about health inequalities outlined above, it concluded that it was not appropriate to apply a stopping rule based on entry to residential care.

Stopping rule based on disease progression

3.17 The second stopping rule used in the company's base case assumed that people stop treatment once their condition has progressed to moderate dementia caused by Alzheimer's disease. This is aligned with the marketing authorisation for lecanemab. The clinical experts noted that there are no clear guidelines on how progression to moderate disease is defined (see section 3.2). At the second committee meeting, the company shared views from 3 clinical experts that said monitoring would not be resource intensive. But it shared a scenario analysis in which quarterly (3-monthly) outpatient appointments were included. The EAG adopted this scenario in its base case, explaining that monitoring costs should be included. The commissioning expert explained that people are currently

discharged from follow up after a diagnosis of early dementia. This means that people with early dementia must return to primary care once their dementia worsens to be referred to specialist care. So, additional resources would be needed because monitoring and functional assessments (especially CDR-SB) are not standard practice. The clinical experts estimated that people having lecanemab would be routinely monitored every 6 months. They added that monitoring for disease progression could also be done every 6 months, so a progression-based stopping rule would not lead to additional monitoring being needed. They added that functional assessments could be carried out during routine lecanemab infusions. They noted that there might be some variation in clinician interpretation of the questionnaire results, but no additional resource would be needed. The commissioning expert commented that nurses would need additional training to carry out the functional assessments. They added that people with Alzheimer's disease who stop treatment because of disease progression might find this challenging. So, additional resources may be needed to support them and their carers.

At the third committee meeting, the company reiterated that no additional resources would be needed to monitor disease progression. But it did share a scenario including 6-monthly outpatient visits to reflect uncertainty. The EAG considered that functional assessments likely need more staff time, or time for different staff, than infusion visits. So, it included 6-monthly outpatient appointments in its base case. The committee noted clinical expert opinion that disease progression should be monitored for every 6 months. So, the committee concluded that 6-monthly outpatient visits should be included to reflect the resource impact of monitoring for disease progression.

Treatment discontinuation

3.18 The company's model assumed that all-cause treatment discontinuation was constant over time and was derived from Clarity AD data. At the first committee meeting, the EAG noted that it was unclear whether it was

appropriate to assume a constant rate of stopping from Clarity AD after 18 months. At the second committee meeting, the company presented a scenario in which the all-cause discontinuation rate for lecanemab after 18 months was based on 36-month data from the Clarity AD open-label extension (OLE) study. It also shared data from Clarity AD OLE that showed the average amyloid level was below the 30 centiloids threshold for amyloid negativity after 18 months of lecanemab treatment. The committee thought that it was appropriate to base the discontinuation rate on the more mature data. So, it preferred to use the data from Clarity AD OLE for discontinuation rates after 18 months.

Treatment effect waning

3.19 At the first committee meeting, the company assumed that there was no waning of treatment effect while on treatment with lecanemab. It assumed that people who stopped treatment because of progression to moderate or severe dementia caused by Alzheimer's disease had treatment effect waning after they had stopped. The exact estimate for treatment effect waning is considered confidential by the company and cannot be reported here, but it was based on the estimated rate of amyloid re-accumulation. The clinical experts noted that it is highly implausible that a person's condition will immediately worsen after stopping treatment with lecanemab. They added that amyloid levels do not suddenly revert to baseline levels on stopping treatment, saying that this could take years, but that this is uncertain. But the clinical experts noted that the relationship between level of amyloid plaques and symptoms of Alzheimer's disease is unclear. The committee thought that the company's estimate for treatment effect waning was uncertain because it was based on the estimated rate of amyloid re-accumulation. Also, it noted there is uncertainty in the link between amyloid re-accumulation and disease symptoms.

The company assumed that treatment effect was not lost in people who stopped treatment in the MCI and mild dementia caused by Alzheimer's

disease health states because of all-cause discontinuation. It justified this approach because the Clarity AD data used in the model (and the hazard ratio applied to transition probabilities; see section 3.13) related to the intention-to-treat population. This meant that discontinuations were accounted for in the efficacy data. The company further explained that no-one in Clarity AD was recorded as stopping treatment because of an inadequate treatment effect. The company noted that the EAG involved in NICE's technology appraisal guidance for donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease did not apply treatment effect waning. But the EAG for this evaluation thought that it was unsuitable to assume a persistent treatment effect for people who stopped treatment in the MCI and mild dementia caused by Alzheimer's disease health states. It explained that people who stop lecanemab may still lose treatment response, even if that was not the reason for stopping. It also shared a scenario that assumed an arbitrary 75% treatment effect for people who stop treatment in the MCI and mild dementia caused by Alzheimer's disease health states. The committee concluded that it was inappropriate to assume that people who stopped treatment in the MCI and mild dementia caused by Alzheimer's disease health states continued to have the same treatment benefits as people who remained on treatment. But it also thought that it was inappropriate to assume treatment benefits would be lost immediately and completely after stopping treatment. It noted that scenarios exploring this assumption by the company and EAG were based on arbitrary figures, not on robust clinical expectations. But it thought that the most appropriate approach would include some treatment effect waning, which was not aligned with the company's base case. The committee thought that the rate of treatment effect waning for people who stopped treatment on progression to moderate or severe disease was also uncertain.

At the third committee meeting, the company updated its base case in response to the committee's preferences and expert opinion. It included

treatment effect waning for all people who stopped treatment, with waning increasing linearly to 100% at a timepoint aligned with amyloid re-accumulation rate. Treatment effect waning was based on the following:

- Waning started when the amyloid level was 30 centiloids (amyloid negative threshold).
- No treatment effect (100% treatment waning) was modelled when amyloid levels were 50 centiloids.
- The amyloid re-accumulation rate was 2.6 centiloids per year (based on a study by Swanson et al. [2021]).
- Other data points related to the treatment waning assumptions are considered confidential by the company and cannot be reported here.

The EAG thought that the company's updated approach to treatment effect waning was uncertain. This was because it is uncertain whether treatment effect is directly linked to amyloid clearance. Also, the modelled amyloid re-accumulation rate was from a study with a small sample size and very limited follow up. This meant the re-accumulation rate could have been underestimated because the duration for which off-treatment amyloid re-accumulation was observed, and the number of people monitored, was unknown. The EAG's base case included treatment effect waning based on time since treatment discontinuation rather than rate of amyloid re-accumulation. It was based on:

- When people stopped treatment before 18 months in the model, treatment effect waning began immediately and took 4 years to reach full loss of treatment effect. This aligned with committee preferences at the second committee meeting for the evaluation of donanemab for treating MCI or mild dementia caused by Alzheimer's disease.
- When stopping treatment after 18 months, waning started 1 year after of stopping and took 4 years to reach full loss of treatment effect. But the EAG considered that this was optimistic.

The committee noted the efforts of the company and EAG to address its concerns around treatment effect waning. It understood the company's approach based on amyloid re-accumulation. But it recalled that there was uncertainty in assuming the lecanemab treatment effect was directly linked to amyloid clearance. The committee noted that the treatment effect waning after stopping lecanemab was unknown. This was because there was no randomised evidence on clinical effectiveness in people who had taken lecanemab compared with placebo, after 18 months in the trials. It also noted that, because of the mixed pathology of Alzheimer's disease, which may include increasing tau levels, it is also uncertain whether waning would be linear. So, the committee concluded that the EAG's approach to modelling treatment effect waning based on time since treatment discontinuation was acceptable for decision making, but highly uncertain.

Costs

Infusion costs

3.20 At the first committee meeting, the company's model assumed that the administration cost of each lecanemab infusion was £208. This was based on the SB12Z tariff cost in the 2021 to 2022 National Tariff Payment System, uplifted to reflect current prices. The code relates to a simple parenteral chemotherapy first infusion. The company explained that this code was the most appropriate for estimating lecanemab infusion costs in the absence of an exact infusion cost estimate for lecanemab for Alzheimer's disease. This was because lecanemab is administered as a 1-hour infusion, alongside about 30 minutes of nurse time. Submissions from NHS England identified a different cost that it thought was most suitable. This 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'. The clinical experts explained that they would expect the infusion cost to be close to the £208 value

suggested by the company. Their experience of lecanemab was that of a similar infusion time and monitoring to that of chemotherapy treatments. The patient and clinical experts added that the infusion of lecanemab is not complex and does not need intensive monitoring.

At the second committee meeting, the company shared the results of a microcosting study it did with 3 healthcare professionals with lecanemab experience to estimate associated resource use. The resulting estimated infusion cost was £139. NHS England explained that a breakdown of infusion resource costs for lecanemab could not be provided. This is because lecanemab is not used in clinical practice and resources used in the trial were not relevant to the NHS. NHS England estimated an infusion cost of £432. This was estimated using a bottom-up costing approach based on real-world costs. This was the same approach that had been used to estimate infusion costs for monoclonal antibodies as treatment for COVID-19. It advised against using a chemotherapy infusion cost because lecanemab:

- is more complex to prepare
- has the potential for more adverse reactions
- people having it might have more complex needs than people having chemotherapy infusions.

The clinical experts explained that lecanemab is delivered as efficiently as chemotherapy. They also expected that the needs of the population would be similar because people with more advanced disease who are frail and need additional care would not be eligible for lecanemab. But the commissioning expert explained the efficient drug administration seen in the trial setting may not be replicated in the real world. The committee asked the company why its microcosting approach only included 30.8 minutes of healthcare practitioner time when the infusion takes 1 hour with an additional 30 minutes of observation time. The company and clinical experts explained that 1 nurse can supervise

multiple infusions at once. Also, people do not need constant observation during the infusion. The commissioning expert outlined that the microcosting study did not include background infrastructure costs and opportunity costs that HRG code costs include. The committee was aware of section 4.4.10 of NICE technology appraisal and highly specialised technologies guidance: the manual. It outlines that data on HRGs may not always be appropriate, and other evidence sources such as microcosting studies may be more appropriate. But the manual states that, in all cases, all relevant costs such as testing, follow up, treatment, monitoring, staffing, facilities, training and any other modifications should be included.

At the second committee meeting, the committee concluded that the methodology provided for the company's microcosting approach was vague. So, it may not have accurately included monitoring, staffing, facilities and training costs. It also thought that the scope of the study was limited because only 3 people were consulted to estimate resource use and their answers varied considerably. It also concluded that the preferred cost from NHS England was not specific to lecanemab and did not reflect the expected resource needs outlined by clinical experts. It also noted a lack of transparency on how the cost from NHS England was estimated and how it related to specific lecanemab resource needs. So, it was unable to determine a preferred cost for use in modelling.

At the third committee meeting, the company continued to use its microcosting study to estimate the infusion cost of lecanemab. It explained that the microcosting approach included Personal Social Services Research Unit unit costs for overheads and capital overheads, weighted for shared use of space. But the company acknowledged that 30.8 minutes of healthcare practitioner time may not reflect the full costs of a 1-hour infusion. So, it shared a scenario that included

overhead costs for a full hour. The company critiqued the NHS England cost. It explained that it was not appropriate because it included a 10% uplift to account for costs related to COVID-19. Specifically, the estimate included costs for establishing temporary COVID-19 medicines delivery units, which should not be included for lecanemab. It also challenged the lack of transparency in the NHS England estimated cost. The EAG noted that infusion-related reactions and the complex needs of some people having lecanemab were not included in other cost estimates. So, the EAG's base case included the NHS England infusion cost. For the third committee meeting, NHS England provided a breakdown of how it estimated the infusion cost:

- It searched for the average price for an infusion of a monoclonal antibody across multiple indications from the NHS England secondary user services dataset. The search resulted in an estimated cost of £361 for the year 2021 to 2022.
- It increased this figure by 10%, as had been done when deriving a tariff for delivering monoclonal antibodies for COVID-19. This is because the additional needs for people with Alzheimer's disease are considered to have similar resource implications as delivering treatments for people with COVID-19. This was further inflated to 2024 to 2025 prices and a market forces factor was applied, totalling £462.

NHS England noted that this estimate was higher than its preferred estimate of £432 because of updated inflation figures since the initial calculation. It also showed that rerunning the search and using 2023 to 2024 prices inflated to 2024 to 2025 would produce a cost of £489. So, NHS England considered that £432 was at the lower end of the range of the potential estimates for infusion costs. The company outlined that there was considerable heterogeneity in the data entries included in the NHS England estimate, with some outliers that skewed the cost. It said that restricting the search to codes with 50 or more entries reduced the estimated cost to roughly £300. The NHS England representative noted

that there are inevitable outliers in the data. They explained that the SB12Z code also included heterogeneity because it was sourced from multiple entries. The NHS England representative further explained that they had carried out the usual calculations for when a tariff for a service does not exist (such as a lecanemab infusion). They noted that their estimate was lower than the infusion costs for monoclonal antibodies in multiple sclerosis, such as natalizumab, which is over £500. These treatments also target the brain, and the populations might have similar needs. The committee acknowledged that there was uncertainty in the cost of infusion because lecanemab is a new class of treatment that is not currently available in the NHS. It carefully considered all the evidence it had seen on infusion costs over the 3 committee meetings. It noted the large impact that the estimates had on the ICER, including whether the ICER would be considered cost effective or not. The committee concluded that its preferred infusion cost must reflect the costs incurred in real-world practice as much as possible. So, it preferred the £432 cost estimated by NHS England because this cost is most likely to reflect what would be charged in NHS practice. But it acknowledged this estimate was uncertain.

Private care costs

3.21 The company's submission for the first committee meeting included an estimate of direct non-medical costs to account for social care costs, such as residential care and home-based community care costs. It used costs estimated by Alzheimer's Society research in 2014, and adjusted them to reflect current prices. At clarification, the EAG questioned what proportion of the estimated costs related to private care and so would be outside of the cost perspective set out in the NICE reference case. The company responded that the costs did include private care costs, but the proportion was not identified by the authors. It provided a scenario analysis that assumed an arbitrary 10% of the costs were private and excluded these costs. The EAG noted that, elsewhere, the Alzheimer's Society had estimated that two-thirds of annual dementia costs are currently paid by

people with dementia and their families. This is either in unpaid care or in paying for private social care. So, the EAG provided a scenario that assumed two-thirds of the costs used by the company were paid for privately and so excluded these costs. But it noted that the excluded costs were likely to be too high because the cost used by the company did not include unpaid care.

For the second committee meeting, the company used the figure cited by the EAG to estimate the proportion of non-medical costs that were paid for privately. So, it excluded the estimated private care costs from the model. It made the adjustment in a scenario analysis that reduced non-medical health-state costs by 47.2%. The EAG agreed with the company scenario and adopted it in its updated base case. The committee noted that the NICE reference case states that costs should relate to NHS and personal social services resources, and should be valued using the prices relevant to the NHS and personal social services. So, it thought that it was appropriate to remove the proportion of costs that would be paid for in private care from the company's estimate of direct non-medical costs.

At the third committee meeting, the company updated its base case to include an alternative estimate of health-state costs to align with the committee's preferences at the second committee meeting for the evaluation of donanemab for treating MCI or mild dementia caused by Alzheimer's disease. The company used health-state costs from Wittenberg et al. (2019) because they did not include private care costs, as per the committee's preference. The committee concluded that using the Wittenberg et al. costs was appropriate and used these costs for decision making.

Amyloid beta testing costs

3.22 Treatment with lecanemab is conditional on confirmed amyloid beta pathology. So, the company included the diagnostic testing costs in its base case. It did this by assuming that 90% of people would have a

lumbar puncture to test their cerebrospinal fluid and 10% would have a PET-CT scan. The company also included costs for people who would have tests but would not have lecanemab. It assumed 28.8% of people tested would not be eligible for treatment, based on screening in Clarity AD. The EAG's clinical expert agreed that 90% of people would have a lumbar puncture and 10% of people would have a PET-CT scan. But the EAG used a higher screening failure rate of 43.1% in its base case. This was based on a report by the NICE Health Technology Assessment lab that estimated the eligible population for lecanemab. The clinical experts indicated that they would expect a screening failure rate of about 20% in NHS clinical practice. NHS England agreed, explaining that it used a screening failure rate of 20% in its eligible population calculations. The committee concluded that it was appropriate for the company to assume that 90% of people tested for amyloid beta would have a lumbar puncture and 10% would have a PET-CT scan. It also concluded that it was appropriate to assume that 28.8% of people who have tests for amyloid beta would not have amyloid pathology, so would not be eligible for lecanemab.

APOE4 testing costs

3.23 The marketing authorisation indication for lecanemab stipulates that people are eligible for treatment if they are heterozygous for APOE4 or do not have the gene (see section 2.1). So, the economic model included costs for APOE4 testing, as well as an outpatient appointment and genetic counselling. At the first 2 committee meetings, these costs were based on the budget impact submission from NHS England. The APOE4 testing cost included was £250. But for the third committee meeting, the company updated the cost of APOE4 testing in its base case to a cost from the Scottish Health Service (£41.10, R130 Laboratory Services for Clinical Genetics). This was because the testing cost provided by NHS England could not be verified. The EAG agreed that the cost identified in Scotland was relevant and included it in its base case. NHS England explained that the estimated testing cost was based on a comparable test available in

England. The committee concluded that the modelled costs must reflect the costs incurred in real-world practice as much as possible. So, it preferred to use the cost provided by NHS England. The committee also noted the very small impact that this change had on the ICER.

Utility values

Utility values used in the model for people with Alzheimer's disease

3.24 At the second committee meeting, the company's approach to utilities included a mixed effects model with repeated measures with backward elimination. The model was based on EQ-5D data from Clarity AD. The company used this model to address the EAG's concerns that using mean EQ-5D values did not take into account variation between people, potential confounding variables and changes to utility over time. The EAG noted that it was unable to fully assess the company's implementation of the mixed effects model with repeated measures because insufficient information was provided. But it thought that it was appropriate to use this model in its base case. The EAG removed the fixed effects treatment covariate in the utility model. The committee concluded that it was appropriate to use the mixed effects model with repeated measures to estimate utilities. The company used proxy-reported estimates for all health states because the estimates for patient-reported utilities were inconsistent. It also provided a summary of the adaptation effect in utility values for Alzheimer's disease. The adaptation effect is seen when people with chronic health conditions adapt to the symptoms of their condition and do not record their quality of life relative to perfect health. This results in patient-reported quality-of-life estimates that are lower than general population or carer-reported estimates for the same condition. The company's literature search found that adaptation is not well understood. But it may contribute to differences in quality of life in the early stages of Alzheimer's disease. The company noted that differences in later stages are likely caused by neurological deterioration and not adaptation.

The company did scenario analyses to show that the cost-effectiveness results were not sensitive to using proxy utility values. The EAG's base case used patient-reported EQ-5D scores for the MCI and mild dementia health states. The committee noted that NICE technology appraisal and highly specialised technologies guidance: the manual 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, they should come from carers. The committee noted that it is not known at what level of severity of Alzheimer's disease people are unable to accurately self-report quality of life. It also noted that using patient-reported or proxy utility values had a very small effect on the cost-effectiveness results. So, the committee accepted the EAG's proposed approach of using:

- patient-reported EQ-5D scores for the MCI and mild dementia health states
- proxy-reported values for the moderate and severe dementia health states
- treatment-independent utility values.

At the third committee meeting, the company updated its base case to include the committee preference for using patient-reported EQ-5D scores for the MCI and mild dementia health states. It also used utility values that were treatment independent, in line with committee preference. The company also updated its base case to include disutility for serious and severe adverse events. This was in response to the EAG's concern that it was inappropriate to assume that the disutility of adverse events was already captured in the Clarity AD data. Quality-of-life data was collected in 6-monthly intervals. This meant that some adverse events were likely to have occurred and resolved in that time and not be reflected in the data. The EAG commented that the company's inclusion of serious or severe adverse events only partially resolved its concerns. This was because lower-grade adverse events

were not modelled. Also, the durations of adverse events that were modelled may have been too short. So, the EAG was still concerned that disutility from adverse events was underestimated. The committee concluded that the company's approach to including adverse event disutility was suitable for decision making but associated with uncertainty.

Utility values used in the model for carers

3.25 Utility values for carers were taken from the literature and modelled as a function of the health state of the person with Alzheimer's disease. At the second committee meeting, the company updated its base case to use an incremental approach to model carer utility. This approach used the worst alive health state (severe dementia in residential care) as a reference. Increments were calculated relative to this health state for other health states. This approach avoided the carer QALY trap in which extended survival time is penalised because lower carer utility when a person is alive is modelled for longer. In the company's base case, utility values for people with Alzheimer's disease and carers were also adjusted when a person with Alzheimer's disease entered residential care. It included a disutility of 0.09 for carers of people in residential care. The company also thought that carer health-related quality-of-life effects were underestimated. This was because the EQ-5D does not accurately capture carer health-related quality of life in Alzheimer's disease, and the model only assumed 1 carer per person. The EAG's base case maintained the company's incremental approach to estimating carer health-related quality of life. But the EAG removed the difference in carer utility for the same health states but in residential and community care. The committee thought that the company's updated incremental approach to carer QALYs was reasonable and preferred to use it for decision making.

At the third committee meeting, the company stated again that the EQ-5D underestimates carer health-related quality of life in Alzheimer's disease.

It shared evidence that showed a greater estimated quality-of-life impact on carers when using the Zarit Burden Interview tool instead of the EQ-5D. The company did a scenario analysis in which it applied the utility difference between MCI and other health states from a vignette study to MCI carer utility from Clarity AD. The company assumed there were 1.8 carers for each person with Alzheimer's disease. The company explained that the approach was consistent with the company approach in the evaluation of donanemab for treating MCI or mild dementia caused by Alzheimer's disease. The company's base case continued to assume an additional disutility of 0.09 for carers of people in residential care. The EAG agreed that the health-related quality-of-life impact on carers may be underestimated when using the EQ-5D and modelling only 1 carer. So, in its base case the EAG included 1.8 carers. It also removed the utility decrement for people in residential care. The committee noted that its preferred approach in the evaluation of donanemab for treating MCI or mild dementia caused by Alzheimer's disease was to use 1.8 carers and utility values from the GERAS study. It noted that GERAS was a large study giving UK-relevant estimates and appeared reasonable. It also noted that in the GERAS study each person with Alzheimer's had an average of 1.8 carers.

The committee noted that, although quality of life and health-related quality of life are sometimes used interchangeably by patients and carers when describing the impact of a disease or condition, NICE's methods specifically incorporate health effects (only) in the QALY calculation. It also noted the impact on carer health effects was being multiplied 1.8 times (for number of caregivers), for every 1 person. So, the committee concluded it was appropriate to use the utility values from GERAS as well as 1.8 carers for each person with Alzheimer's disease. It also concluded that it was not appropriate to apply an additional utility decrement for carers of people in residential care. This was because it had not seen evidence to indicate that the decrement was suitable. The

committee noted that section 4.36 of NICE technology appraisal and highly specialised technologies guidance: the manual states that 'given the need for consistency across evaluations, the EQ-5D measurement method is preferred to measure health-related quality of life in adults'. Section 4.3.10 of the manual provides guidance for the supportive evidence that should be provided to make a case that the EQ-5D is inappropriate. The committee acknowledged that it was uncertain whether EQ-5D was appropriate for measuring health-related quality of life for carers of people with Alzheimer's disease. But it thought that the company had not provided the supportive evidence listed in the manual and requested it to do so. The committee concluded that it would like to see further sources of health-related quality-of-life evidence for carers of people with Alzheimer's disease.

Severity

3.26 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee can apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity that meet the threshold for absolute and proportional QALY shortfalls. The company provided absolute and proportional QALY shortfall estimates in line with NICE technology appraisal and highly specialised technologies guidance: the manual. But the values did not meet the threshold for a severity weight greater than 1 to be applied to the QALYs. So, the company, EAG and committee agreed that lecanemab did not meet the threshold for a severity weight. The committee recalled the powerful testimony from patient experts and considered the significant impact of Alzheimer's disease on people with the condition and their carers. But the committee recalled that the absolute and proportional QALY shortfall thresholds were not met in the company's and EAG's base cases. So, it concluded it should not apply a greater weight to the QALYs.

Cost-effectiveness estimates

Committee's preferred assumptions

3.27 The committee concluded that the cost-effectiveness modelling for lecanemab compared with placebo was uncertain. But it was able to determine its preferred assumptions for the modelling after draft guidance consultation responses from the company and other stakeholders. The committee noted that, overall, there was a lot of uncertainty with its preferred assumptions, but they were:

- using the company's overall model structure (see section 3.10)
- modelling backward transitions (that is, transitions to a better health state) (see section 3.12)
- using the multistate survival analysis to estimate transition probabilities that changed over time for the first 18 months in the model (see section 3.13)
- using the general population mortality for the MCI subgroup (see section 3.14)
- lecanemab would not affect the proportion of people who moved directly from mild dementia to severe dementia compared with standard care (see section 3.15)
- not including a stopping rule based on entry to residential care (see section 3.16)
- including 6-monthly outpatient visits to reflect the resource impact of monitoring for disease progression (see section 3.17)
- when people stopped treatment before 18 months, treatment effect waning would be immediate with a 4-year duration, and when stopping treatment after 18 months, waning would start 1 year after stopping and last for 4 years (see section 3.19)
- using NHS England's estimated infusion costs (£432, see section 3.20)
- using Wittenberg et al. (2019) health-state costs (see section 3.21)
- 90% of people having tests for amyloid beta would have a lumbar puncture and 10% would have a PET-CT scan, and 28.8% of people

who have tests for amyloid beta would not have amyloid pathology (see section 3.22)

- using NHS England's estimated APOE4 testing costs (see section 3.23)
- using the mixed effects models with repeated measures to estimate utilities (see section 3.24)
- using patient-reported EQ-5D scores for MCI and mild dementia health states (see section 3.24)
- treatment-independent utility values (see section 3.24)
- using the incremental approach to modelling carer utility (see section 3.25)
- including 1.8 carers and the utility values from GERAS, and removing the utility decrement for people in residential care (see section 3.25).

Cost-effectiveness estimates

3.28 NICE technology appraisal and highly specialised technologies guidance: the manual notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, even where it has been able to specify preferred assumptions. The uncertainty included:

- the duration of the lecanemab treatment effect (see section 3.6)
- differences in the treatments used in Clarity AD and NHS clinical practice (see section 3.7)
- the potential impact of patient heterogeneity on the treatment effect (see section 3.10)
- the likely proportion of people starting lecanemab with MCI or mild dementia caused by Alzheimer's disease (see section 3.11)

- how long the full treatment effect of lecanemab is maintained then wanes after stopping treatment (see section 3.19)
- the cost of lecanemab infusion because it is a new class of treatment not currently administered in the NHS (see section 3.20).

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained. It noted that there were both uncaptured benefits, and costs or harms, of lecanemab (see section 3.31). So, it did not think that there were strong reasons to change the acceptable ICER from around £20,000 per QALY gained. The company's deterministic base-case ICER for lecanemab compared with placebo was £29,706. The EAG's base-case deterministic ICER was £82,719. The committee's preferred assumptions (see section 3.27) resulted in a ICER of £81,163. The committee noted that, in all estimated ICERs, the estimated QALY gains were small. It also noted that administration costs contributed to a large proportion of incremental costs when using its preferred assumptions. The company noted that, for some combinations of assumptions that included the NHS England infusion cost, lecanemab may not be cost effective even at very low or zero cost. The committee was aware that section 4.4.16 NICE technology appraisal and highly specialised technologies guidance: 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 to be applicable for this evaluation. This was because the non-drug costs largely related to treatment administration rather than the costs of prolonging time in expensive health states. The committee concluded that it could not recommend lecanemab for routine use. This was because the ICER with the committee's preferred assumptions applied was considerably above the range normally considered cost

effective. The committee noted that section 6.2.33 of NICE technology appraisal and highly specialised technologies guidance: 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 people based on the level of decision uncertainty and whether this could be mitigated. The committee noted that only a small benefit to people was shown in the trial. It also noted that substantial resources would be needed to implement access to lecanemab in the NHS and that this may affect the provision of other services (see section 3.31). It decided the decision risk was too great to recommend lecanemab.

Managed access

Managed access not recommended

3.29 Having concluded that lecanemab could not be recommended for routine use, the committee then considered whether it could be recommended with managed access for treating MCI and mild dementia caused by Alzheimer's disease. NHS managed access is a time-limited agreement. It allows people to access new treatments while further evidence is gathered. It is a way to address uncertainties about a drug's clinical and cost effectiveness. The company proposed that data could be collected from the OLE of Clarity AD. It also updated its managed access proposal for the second committee meeting, which included details that are commercial in confidence and cannot be reported here. The managed access team at NICE commented that the updated managed access proposal meant that some of the key uncertainties may be resolved during a period of managed access. But some key issues, such as treatment discontinuation and infusion costs, may not be resolved. The clinical lead for the Innovative Medicines Fund highlighted concerns about lecanemab meeting the necessary criteria for a recommendation in managed access. Specifically, the cost-effectiveness estimates in the EAG's base case and

the most plausible ICER identified by the committee were not cost effective. Also, there were significant concerns that proposed collection of real-world data in the NHS would lead to considerable burden. They also thought that there were considerable uncertainties that further data collection may not address. The committee noted that the managed access proposal did not include any new randomised controlled trial data for lecanemab in people with MCI and mild dementia caused by Alzheimer's disease. This meant that there would be no new direct evidence available for the relative treatment effectiveness of lecanemab compared with standard care, so this was likely to remain uncertain. For the third committee meeting, the company did not update its managed access proposal. Instead, it disagreed with the view that the proposed collection of real-world data in the NHS would lead to considerable burden. The committee recalled that the most plausible ICER was likely to be considerably above the range normally considered cost effective. It also thought that a key driver of these results was the small clinical benefit of lecanemab. It understood that data collected in managed access was unlikely to show a substantially greater clinical benefit for lecanemab than that estimated in the committee's preferred base case. So, the committee concluded that lecanemab did not meet the criteria to be considered for a recommendation with managed access.

Other factors

Equality and health inequality issues

3.30 Submissions from the company and experts identified potential equality and health inequality concerns for consideration. The issues identified were:

- There is current inequality in terms of who has an Alzheimer's disease diagnosis and accessing care. This will be worsened by introducing the complex diagnostic pathway for lecanemab.

- People with Down's syndrome (who have a more than 90% lifetime risk of developing Alzheimer's disease), people with young-onset dementia and people from different ethnic minority backgrounds were not fully represented in Clarity AD. These groups are at risk of being excluded from accessing lecanemab.
- Lecanemab may have different treatment effectiveness and benefits for different subgroups based on age, sex and family background.
- Lecanemab would need significant increases in NHS capacity for service delivery. Inequalities may increase as existing services that are already under strain would be needed to deliver the treatment.

The committee noted the concerns raised with getting a diagnosis, accessing care in a new and complex pathway, and substantial demand on NHS services. It understood these concerns but noted that 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 the possibility of different treatment effects for subgroups. 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

3.31 Stakeholder submissions throughout the evaluation identified potential uncaptured benefits and harms of lecanemab. The potential uncaptured benefits of lecanemab raised were:

- Utility values may have been underestimated by using patient-by-proxy-reported quality-of-life data.
- The impact on the finances and productivity of carers for people with Alzheimer's disease were not captured in the model. The committee noted that these costs fall outside of the NICE reference case.

- Lecanemab is innovative, as shown by its designation to the Innovative Licensing and Access Pathway by the Medicine and Healthcare products Regulatory Agency.
- Lecanemab is not eligible for the severity modifier despite:
  - Alzheimer's disease being the leading cause of death in the UK
  - the condition causing a significant disease burden
  - clinical consensus that treating milder Alzheimer's disease states is more beneficial than treating more severe disease states.

  The committee noted that eligibility for a severity modifier is defined in the NICE manual as absolute and proportional QALY shortfalls meeting specific thresholds. These estimates quantify the future health of people with a condition by comparing it with general population length and quality of life that is adjusted for age and sex. Based on both the company's and EAG's preferred model assumptions, lecanemab does not meet the criteria for a severity modifier. The potential uncaptured harms of lecanemab raised were:

- false hope for people who are not eligible for lecanemab, or who may find out they are APOE4 carriers and may experience worse outcomes than others
- false hope that treatment with lecanemab leads to large clinically significant slowing of disease progression compared with not treating with lecanemab
- false hope for people who believe that lecanemab is a cure for Alzheimer's disease and not only a treatment that modestly slows disease progression
- harms of repeated diagnostic testing and monitoring
- 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 lecanemab may increase or decrease the most plausible ICER. But it noted that it had not been presented with any information to incorporate the uncaptured aspects into the cost-effectiveness estimates. So, the committee was unable to reach a conclusion on the impact of uncaptured benefits and costs.

Conclusion

Recommendation

3.32 The committee acknowledged the significant unmet need for treatment options to prevent progression to mild dementia caused by Alzheimer's disease. It also noted that the most plausible cost-effectiveness estimate was considerably above the range normally considered a cost-effective use of NHS resources. The committee decided that the small 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 lecanemab, 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, the committee did not recommend lecanemab for treating MCI and mild dementia caused by Alzheimer's disease in adults who are heterozygous for APOE4 or do not have the gene, 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

Dr Megan John and Dr Raju Reddy

Chair and vice 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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