Single Technology Appraisal

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance 2 from Eisai**
   a. Comments
   b. Comments appendices

2. **Consultee and commentator comments on the Draft Guidance 2** from:
   a. Alzheimer's Research UK
   b. Alzheimer's Society
   c. Association of British Neurologists
   d. Royal College of Psychiatrists
   e. UK Clinical Pharmacy Association
   f. UCL Dementia Research Centre
   g. NHS England Infusion cost estimate

3. **Comments on the Draft Guidance 2 received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance 2**
   a. EAG critique
   b. EAG addendum to critique

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments **5pm** on **Thursday 27 March 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eisai

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Introduction** Eisai (henceforth referred to as 'the company') welcomes the opportunity to comment on the draft guidance, resolve outstanding uncertainty, and secure access to lecanemab for eligible NHS patients in England and Wales.

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	Lecanemab is the first treatment that targets an underlying cause of early Alzheimer's disease (AD) to be authorised in a country in Europe.[1] This represents a step-change in the treatment of early AD, particularly for patients with mild cognitive impairment (MCI) due to AD, for whom there are currently no pharmacological treatment options. The company understand that the introduction of lecanemab as an innovative treatment is associated with significant system change in the UK. **Base case analyses** The company has updated the economic model base case to allow the committee to make an informed judgement on the cost-effectiveness of lecanemab. Changes to the model address remaining uncertainties by aligning with committee preferred assumptions or the concurrent appraisal of donanemab for MCI and mild dementia caused by AD (NICE ID6222) where these reduce or resolve uncertainty or better reflect current UK practice. Updates to the economic model included in the base case consist of: • Updated baseline distributions of patients across MCI and mild AD health states (20.4%:79.6%) to better reflect current UK practice, in line with committee preference in NICE ID6222 (comment 2) • Updated number of caregivers per patient (1.8), in line with committee preference in NICE ID6222 (comment 2) • Use of the health state costs from Wittenberg et al. 2019 to avoid assumption on the proportion of non-medical costs attributable to private care, in line with committee preference in NICE ID6222[2,3] (comment 2) • Applying treatment waning to all off-treatment health states, in line with committee preference, regardless of reason for discontinuation, using mean amyloid positron emission tomography (PET) levels from Clarity AD and amyloid re-accumulation rates (comment 4) • Use of patient-reported EQ-5D (using a mixed model for repeated measures [MMRM]) for MCI and mild dementia health states in line with committee preference (comment 7) • Use of general population mortality for MCI (HR=1) in line with committee preference • Use of Scottish Health Service APOE4 testing costs[4] due to the absence of verifiable costs in England (comment 9) In addition, the company has proposed a revised Patient Access Scheme (PAS) (Appendix A.2.4), in the form of a simple discount, which demonstrates the cost-effectiveness of lecanemab and a substantial commitment by the company. The revised base case and increased PAS, as shown in Appendix A.2.4.1, Table 8, yields a cost-effective ICER of £29,706 per QALY. **Scenario analyses** The company has also conducted additional scenario analyses (Appendix A.2.4.2.3, Table 12), including:

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	1. Updated micro-costing infusion cost estimate to include overheads associated with chair time (comment 3) 2. Inclusion of the chemotherapy SB12Z HRG code for lecanemab infusion (comment 3) 3. Treatment effect waning for all off-treatment states based on time to return to baseline amyloid PET level ([redacted]) (comment 4) 4. Immediate 0% treatment effect for all off-treatment moderate to severe AD patients, 75% treatment effect for other off-treatment health states to reflect EAG approach (comment 4) 5. 10% of patients remain on treatment following entry into long-term institutional care, addressing committee's concerns on equity of access while reflecting clinical expert feedback that continued treatment for patients with mild AD who permanently enter residential care would be inappropriate (comment 5) 6. Inclusion of six-monthly outpatient visits for lecanemab treated patients to account for uncertainty in the resourcing implications for implementing the stopping rule upon disease progression to moderate AD (comment 5) 7. Use of patient-by-proxy EQ-5D utility values for MCI and mild AD (comment 7) 8. Alignment with NICE ID6222 company caregiver utility values and removal of caregiver disutility on institution (comment 8) 9. Scenario 1 in combination with scenario 8 10. Scenario 2 in combination with scenario 8 11. Removal of caregiver disutility on institution (comment 8) 12. Inclusion of the NHSE APOE4 testing unit cost (comment 9) Additionally, a minor adjustment in column 'AG' of the 'Engine_lec' sheet was made to correct the source of the transition data, which only impacted the model in the one scenario previously presented in which both institutionalisation and severity stopping rules are switched off. This minor adjustment did not impact the base case or scenarios. The results of the scenario analyses using the revised base case indicate that 6 out of 12 scenarios demonstrate cost-effectiveness at a threshold of £30,000 per QALY. In the remaining 6 scenarios, the ICER is below £35,000 per QALY (Appendix A.2.4.2.3, Table 12). These findings highlight the robustness of the economic model and the consistency of cost-effectiveness across a range of plausible assumptions.
2	**Alignment with donanemab appraisal (NICE ID6222)** The company considers there should be consistency in common model inputs across the lecanemab and donanemab appraisals (NICE ID6222), given that the medicines are indicated for identical patient populations (patients with MCI and mild dementia due to AD in adult patients that are apolipoprotein E ε4 [ApoE ε4] heterozygotes or non-carriers). Relevant inputs include the baseline distribution of patients across MCI and mild AD health states, the number of caregivers per patient, and health state costs.

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	1) Baseline distribution of patients across MCI and mild AD health states The diagnosis of eligible patients for lecanemab and donanemab is expected to be the same, thus the baseline distribution of patients across MCI and mild AD health states in the model should be the same. The baseline proportions preferred by the committee in NICE ID6222 were 20.4% MCI and 79.6% mild AD, as per the TRAILBLAZER-ALZ 2 trial.[2] This distribution is consistent with the lecanemab EAG assumption that there would be more people with mild AD than MCI due to AD, and aligns with clinical expert feedback received by the company as part of the response to this draft guidance (March 2025). Feedback from clinical experts suggested that the proportions used in NICE ID6222 were appropriate, and more reflective of current UK practice than the starting proportions of 38% MCI and 62% mild AD assumed by the EAG and adopted in the company's previous base case. The company have therefore adopted these baseline distributions in the revised base case (Appendix A.2.3, Table 7). **2) Number of caregivers per patient** As above, given the indications for lecanemab and donanemab are identical, the number of caregivers per patient is expected to be equivalent. Committee preference in NICE ID6222 was to assume 1.8 caregivers based on the GERAS study, an 18-month, prospective, observational study reflecting the routine care of patients with AD in France, Germany and UK. In the second draft guidance consultation for NICE ID6222, the committee stated "*in line with the GERAS study, assuming 1.8 caregivers is appropriate".* Clinical expert opinion sought in March 2025 by the company confirmed that this assumption was appropriate, with two clinicians confirming the caregiving burden is typically split across family members and that a mean assumption of 1.8 caregivers is reasonable. As noted in response to the first draft guidance consultation, this aligns with the Alzheimer's Research UK (ARUK) patient organisation submission: *"Caregiving is often a shared responsibility among multiple family members, impacting not only the individual and their immediate partner but also other relatives".* The company have therefore aligned with 1.8 caregivers per patients in the revised base case, as opposed to 1 caregiver previously assumed which likely underestimates the impact of AD and lecanemab on caregivers (Appendix A.2.3, Table 7). 3) **Health state costs from Wittenberg et al. 2019** The company acknowledge the committee's conclusion that the current approach to health state costs is appropriate, however this required an assumption that 47.2% of non-medical costs are attributable to private care remains, which is uncertain. Committee preference in NICE ID6222 was to use health state costs sourced from Wittenberg et al. 2019, a study examining the costs of dementia in England. The costs reported by the study do not include any private care costs and hence do not require an assumption to be made regarding these. The company have therefore adopted these health state costs in the revised base case (Appendix A.2.3, Table 7).

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3	**Infusion costs (draft guidance 3.17)** **NHS England cost** While the company acknowledge the committee's conclusion that the estimated cost of lecanemab infusion represents a remaining uncertainty, the company consider the cost provided by NHSE, based on the infusion cost of monoclonal antibodies in the treatment of COVID (£432), to be inappropriate. NHSE recommended this cost as it *"was estimated using a bottom-up costing approach based on real-world costs"*. However, as noted by the committee, the preferred cost from NHSE "*was not specific to lecanemab and did not reflect the expected resource needs outlined by clinical experts"*. Furthermore, there is *"a lack of transparency on how the cost was estimated and how it relates to specific lecanemab resource needs"*. To clarify how this cost was estimated, the company reviewed TA878, in which NHSE suggested the same figure, and note that it includes cost components such as staffing, administrative support, dispensing, clinical consumables, couriering medicines, travel, office equipment, and room hire. These costs are all required for establishing COVID Medicines Delivery Units (CMDUs), which [generally operate from temporary community facilities rather than conventional health care sites] and lack a permanent structure.[5] These satellite service set-up costs should not be attributed to lecanemab. The company also considers that these costs are inappropriate for routine IV delivery of a monoclonal antibody [in an established secondary-care setting]. In addition, NHSE applied a "Market Forces Factor", however the rationale and impact of this adjustment is not provided and is unclear given that it is typically not used in appraisals and is not applied for any other costs in the model. The company has requested clarification from NHSE in relation to its estimated cost of lecanemab infusion including: • An itemised breakdown of the costs included in NHSE's estimated cost of £432 per infusion of lecanemab. • Details of any other assumptions upon which that calculation of estimated cost is based. • Details of the rationale and/or justification for use of the infusion of monoclonal antibodies in the treatment of COVID as the most appropriate reference cost for estimating the cost of lecanemab infusions. However, to date, the above information which is necessary to test the validity and reliability of the figure proposed by NHSE, has not been disclosed. It remains unclear why NHSE is either unwilling or unable to provide transparency regarding its estimated cost of lecanemab infusion. As without this information, stakeholders, including the company, cannot understand and respond to the proposed figure or the committee's conclusion that "*the most appropriate cost was likely closer to the NHSE estimate based on the infusion cost for coronavirus monoclonal antibodies than the company's estimate*". This lack of transparency is inconsistent with standards of procedural fairness, particularly given the fundamental importance of lecanemab infusion costs to the outcome of the appraisal. NICE is aware of the high levels of transparency required in the context of appraisals.

	Therefore, the company urges NICE to ensure that consultees have access to the estimated cost of lecanemab infusion including all the information listed above. Failing this, NHSE's proposed infusion cost estimate should not be considered in the appraisal process. **Simplicity of lecanemab administration** In the absence of an exact infusion cost estimate, clinical expert opinion sought by the company (July 2024) indicated that SB12Z HRG code for chemotherapy administration is an appropriate proxy cost for lecanemab. Their direct experience of lecanemab was that it required a similar infusion and monitoring time to that of a chemotherapy treatment. NHSE consider that lecanemab is more complicated to prepare than chemotherapies. However, no explanation for this conclusion was provided by NHSE and as noted by the committee: "*clinical experts explained that lecanemab is delivered as efficiently as chemotherapy*" and "*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*". Further, the company notes that a clinical expert advised during ACM2 that the pharmacy in their hospital considered that lecanemab was '*too simple*' to make up on an aseptic unit and asked to make it up on the ward, further demonstrating the simple preparation of lecanemab. Moreover, expert statement received in response to the first draft guidance noted that lecanemab infusion "*is no more complex than an infusion of any other drug, and with respect to cytotoxic chemotherapy, significantly less so*". In addition, the company notes that the SB12Z HRG code cost includes 60 minutes of infusion time and 30 minutes of nurse time which align closely with clinician estimates of chair time needed for a lecanemab infusion. NHSE were concerned that lecanemab has the potential for more adverse reactions. However, the cost and utility impact of adverse reactions are already reflected in the economic model. Hence incorporating these into the infusion cost would double count these. Further, the total expected adverse reaction cost for lecanemab in the economic model is £[redacted], inclusive of infusion-related reactions (IRR) and amyloid-related imaging abnormalities (ARIA) of all grades observed during the 18-month randomised period of Clarity AD for lecanemab. The expected cost impact to the service of adverse reactions related with lecanemab infusion is therefore minimal. NHSE believe that patients receiving lecanemab might have more complex needs than patients receiving chemotherapy infusions. However, as noted by the committee: *"clinical experts explained that 1 nurse can supervise multiple infusions at once"* and "*people do not need constant observation during the infusion*". Additionally, the mean age of patients expected to receive lecanemab is 71.8 years (based on the Clarity AD population) while 55% of patients newly diagnosed with cancer in the UK are over the age of 70 (Cancer Research UK), indicating that the mean age is likely very similar between the treated populations. Based on this evidence, the company considers the claims made by NHSE to justify an infusion cost higher than chemotherapy conflict with the available data and are not appropriate for lecanemab. As stated in response to the first draft guidance consultation, the company conducted a hand search of administration costs used for other monoclonal antibodies administered via IV infusion in previous NICE technology appraisals published over the last 6 years (2018-2024). The search identified two appraisals in particular which are consistent with the view that the NHSE proposed cost is an overestimate. Both appraisals evaluated daratumumab; despite having a longer infusion

	duration than lecanemab (3-7 hours vs 60 minutes), the first appraisal (TA763) used a lower administration cost compared with the NHSE cost (£385; SB14Z) and the second (TA897) used a comparable cost (£471; SB15Z). The company therefore reiterate that the NHSE cost is an overestimate of the administration cost for a monoclonal antibody with 60 minutes infusion time. **Micro-costing** In response to a request by the committee during the first draft guidance consultation for a breakdown of resource use for the administration of lecanemab, the company conducted a micro-costing exercise which estimated a cost of £139.12. In the latest draft guidance, the committee state a concern that the micro-costing "*may not have accurately included monitoring, staffing, facilities and training costs."* As per the NICE process and methods manual, the company acknowledge that "*all relevant costs such as testing, follow up, treatment, monitoring, staffing, facilities, training and any other modifications should be included".*[6] The company would like to clarify that unit costs sourced from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care programme, used for the micro-costing, include both overheads and capital overheads. More specifically, overheads include management and other non-care staff costs such as administration and estates staff, as well as non-staff costs such as office, travel/transport, publishing, training courses and conferences, supplies, and services (clinical and general), and utilities such as water, gas and electricity. Capital overheads include overheads based on the new-build and land requirements of NHS hospital facilities, adjusted to reflect shared use of office space for administration, and recreational and changing facilities. The latest draft guidance notes discussion during the second appraisal committee meeting regarding the healthcare practitioner (HCP) time used for the micro-costing exercise, and that one nurse can supervise multiple infusions at once. The company maintain this, however, to ensure that the micro-costing exercise is fully reflective of overhead costs, the company sought additional clinical validation (March 2025) to understand the total chair time associated with lecanemab infusions. Respondents advised an average of 10 minutes of chair time is required for pre-infusion, and that post-infusion time ranges between an average of 37.5 minutes for the first infusion, 22.5 minutes for the second and third infusions, and 10 minutes for the fourth infusion onwards. As the micro-costing exercise already includes 10 minutes of HCP time for pre-drug infusion checks, and 35 minutes of HCP time for post-administration monitoring, the company consider that the micro-costing comprehensively covers the pre- and post- infusion costs and likely overestimates these costs for all but the first infusion. The micro-costing exercise also calculated that an average of 30.8 minutes of active HCP time was required during the 60-minute infusion of lecanemab. Based on feedback received during the second appraisal committee meeting regarding the cost of chair time, the company have updated the micro-costing exercise to include the cost of overheads for the remainder of the 60 minutes not associated with active HCP time (29.2 minutes). This cost was calculated using the proportion of the PSSRU unit cost for a band 5 nurse associated with overheads and capital overheads. Full details can be found in Appendix A.2.1. The updated infusion cost estimated by the micro-costing exercise is £149.26. The company accept there is some variability in HCP responses; however, when conservatively using the highest value from each range for all components, the micro-costing infusion cost is £203.16 which is still lower than the SB12Z HRG code and substantially lower than the cost proposed by NHSE. This implies that SB12Z HRG code is a conservative estimate of the cost of administering lecanemab.

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	In the absence of an HRG code for the intravenous infusion of a monoclonal antibody for AD, and considering the uncertainty associated with the most appropriate proxy, the company has continued to use the micro-costing estimate in the base case. The company believe the micro-costing is fully reflective of all relevant costs specified in the NICE process and methods manual (as noted above) and accurate to the time and staff resource that will be required to infuse lecanemab in NHS practice, based on UK clinical trial experience. Scenarios are presented using the micro-costing estimate inclusive of overheads associated with chair time, and the SB12Z HRG code (Appendix A.2.3, Table 7).
4	**Treatment waning (draft guidance 3.16)** As per the response to the first draft guidance consultation, the company base case conservatively assumed [redacted] for all off-treatment patients upon entry to moderate or severe AD health states and [redacted] for off-treatment MCI and mild AD health states. The company also previously presented a scenario in which [redacted]. The company acknowledge the committee's preference for some treatment waning to be applied for patients who stop treatment in the MCI and Mild AD health states and agree with the committee that an assumption of [redacted] waning for patients who stop upon progression to moderate or severe AD is very conservative. The company also acknowledge the committee's critique that waning scenarios presented by the company and the EAG were based on arbitrary assumptions rather than clinical expectations. Therefore, the company has updated the base case to apply treatment waning to all patients that discontinue, regardless of their reason for discontinuation, with duration of waning based on time taken for amyloid to re-accumulate from different thresholds, to align waning assumptions with observed clinical outcomes. A similar basis for treatment effect waning was used in ID6222. As noted in the response to the first draft guidance document, lecanemab targets amyloid beta and inhibits the amyloid cascade, the trigger for the pathological effects seen in AD. The effects of lecanemab on the amyloid cascade are evidenced through data on amyloid PET levels in Clarity AD (as detailed in Appendix A.1.1; amyloid PET levels reduced to [redacted] Centiloids (CL) in the lecanemab arm of the Clarity AD core study at 18 months, below the 30CL threshold for amyloid negativity in Clarity AD, which is considered a 'normal' level. Amyloid PET levels decreased from baseline through 18 months' time on treatment, as shown in Appendix A.1.1, Table 1. Following the first appraisal committee meeting, the company consulted two experts in August 2024 who indicated they would expect to see a continued treatment effect while amyloid plaque levels remained under the amyloid negativity threshold, with one expert stating that they would expect to see continued divergence in clinical outcomes following discontinuation of lecanemab, given the slow re-accumulation rate of amyloid. Documented amyloid re-accumulation rates following clearance by anti-amyloid therapy range from 2.6CL per year to 3.4CL per year across studies, and align with the estimated natural time course of amyloid accumulation of approximately 3.3CL per year observed in the amyloid-negative stage of AD.[7–11] The model has been revised to reflect the committee's preference and clinical expert opinion. Firstly, in the revised base case, a treatment waning effect is now applied to all discontinued patients, regardless of their reason for discontinuation. This means that patients that discontinue due to all-cause discontinuation, disease severity, or institutionalisation all experience a treatment waning effect. Secondly, it is assumed that waning increases linearly between a start and end timepoint following treatment discontinuation aligned with amyloid re-accumulation, reaching 100% at the end of the duration such that no treatment effect is maintained. The inputs used for amyloid

	level at selected points of treatment discontinuation in the model were taken from Clarity AD. In line with clinical opinion, it is assumed waning starts when the average amyloid level reaches the 30CL threshold for amyloid negativity, and that no treatment effect remains when amyloid levels return to 50CL. The amyloid re-accumulation rate following lecanemab discontinuation was calculated at 2.6CL per year, observed in an off-treatment period in Study 201 and as documented in the lecanemab SmPC.[10] Linking waning to amyloid re-accumulation and assuming no treatment effect remains when amyloid levels reach 50CL is aligned with the committee-preferred assumptions used in ID6222.[12–14] A scenario is explored considering return to baseline amyloid levels ([redacted]) as the point at which no treatment effect remains based on the hypothesis that benefit remains if patients still have lower amyloid levels than at baseline. In order to calculate the starting point and duration of treatment waning, the following methods were applied. [redacted] To avoid the use of tunnel states, which would require extensive structural changes to the model, the company has taken a simplified approach to approximate these waning assumptions. [redacted] The revised base case is aligned with the committee's request to include treatment waning in the base case, and reflects the amyloid re-accumulation observed following lecanemab treatment.
5	**Stopping rules (draft guidance 3.14)** **Institutionalisation** The company acknowledge the committee's conclusion that it would not be appropriate to apply a stopping rule based on entry to institutional care as doing so may lead to increasing inequities. The company do not consider this to be a formal stopping rule but rather a reflection of what would happen in clinical practice. Clinical experts consulted by the company indicate that the reason for entering institutional care should be considered in the decision about stopping treatment; specifically, if patients enter institutional care temporarily for an issue other than their AD, such as their carer needing support, then it may not be appropriate to stop treatment. Accordingly, the source used for the rate of

	institutionalisation in the model, Knapp et al. 2016, excluded care home admissions for respite care from their analysis. Thus, patients who enter institutional care health states in the economic model reflect those requiring permanent, not temporary care. Those who temporarily enter institutional care for respite, and may be able to continue treatment with lecanemab per clinical expert opinion, do not enter institutional care health states and hence, are captured in the community health state occupancy and do not stop treatment. Clinical expert opinion estimated the number of people entering institutional care permanently with mild AD would be extremely small (~5-10%). This is in line with the model which estimates [redacted]% of lecanemab life years spent in institutional care in the MCI or mild AD health states ([redacted] for MCI and [redacted] for mild AD out of [redacted] total life years). Entering care could be due to social reasons where the patient has no caregiver and due to a significant medical comorbidity such as rheumatoid arthritis, is unable to look after themselves at home. One expert noted that continuing treatment in this setting "would not be appropriate", and another described it as "bad practice". Hence, the company maintains that in practice, patients will likely discontinue lecanemab upon entering permanent residential care. Disabling of the institution stopping rule was not discussed at ACM2 but adopted in the EAG's base case, thus informing the committee's preferred assumptions. To reflect the possibility that in UK clinical practice not all patients will cease treatment following institutionalisation for long term care, the company have presented a scenario in which 10% of patients remain on treatment (Appendix A.2.4.2.3, Table 12). This is supported by recent clinical validation sought in March 2025 that 10% of patients entering permanent care are likely to remain on treatment. **Progression to moderate AD** The company believe that no additional resource is required for monitoring progression to moderate AD as clinical expert opinion indicates functional assessments could be carried out during routine lecanemab infusion visits (and hence have no impact on costs). The scenario previously presented by the company, and subsequently adopted by the EAG in its base case, in which patients have quarterly outpatient appointments is therefore considered an overestimate. However, to acknowledge feedback from clinical experts that some patients receiving lecanemab may be routinely monitored every six months and to account for some uncertainty in the specific resourcing implications for implementing the disease-progression stopping rule, the company has updated the scenario to assume six-monthly outpatient visits (Appendix A.2.3, Table 7).
6	**Disabling treatment effect (draft guidance 3.13)** In the committee papers for the second appraisal committee meeting, disabling of treatment effect in mild AD to severe AD transitions was adopted in the EAG's base case. At the second appraisal committee meeting, the company raised the EAG's assumption that lecanemab would not affect the proportion of people who moved directly from mild AD to severe AD as a factual inaccuracy. However, the company were not provided the opportunity to comment further on this assumption during the second appraisal committee meeting, as no discussion took place on issues pertaining to transition probabilities (slide 18 of ACM2 slides). As the committee have identified the proportion of people who move directly from mild to severe AD with lecanemab as an area of uncertainty, the company welcomes the opportunity to explain why disabling treatment effect for lecanemab is inappropriate. It is not appropriate for the time-to-worsening hazard ratio for mild to severe AD to be disabled, as this arbitrarily decreases the treatment effect of lecanemab therefore not reflecting the efficacy

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	observed in Clarity AD. Time to worsening from mild AD was defined as CDR-SB score progressing from mild dementia (4.5-9.0) to moderate or severe dementia (>9.0).[15] In the Clarity AD core study, a treatment effect on the transition from mild to severe AD is observed, as [redacted] patients in the placebo arm transitioned from mild to severe in contrast to [redacted] patients in the lecanemab arm.[15] Therefore, setting the HR for mild to severe AD transitions to 1 is not appropriate as this artificially reduces the treatment effect observed in Clarity AD.
7	**Utility values (draft guidance 3.20)** **Patient-by-proxy utilities** The company believe that proxy-reported utility values are more appropriate than patient-reported values for all community health states due to the difficulties in obtaining accurate self-reported information in this population, and clinical expert opinion (UK HTA advisory board in July 2023 and consultations in March 2025) supported that patient-by-proxy utilities are more objective and should be used at all stages of dementia i.e., for all health states.[16] The company do, however, acknowledge that there is some uncertainty in the level of severity of AD at which patients are unable to accurately self-report quality of life (QoL). As such, the company have adopted patient-reported utilities for the MCI due to AD and mild AD health states in the revised base case, to align with committee preference (Appendix A.2.3, Table 7). **Treatment dependent utilities** In the second draft guidance, the committee expressed a preference for treatment-independent utility values. The patient-reported utilities used for the MCI due to AD and mild AD health states do not differ by treatment group, as treatment was not included as a covariate in the MMRM model. Therefore, by accepting MMRM patient-reported utilities, the revised base case aligns with committee preference for treatment-independent utility values.
8	**Caregiver utility (draft guidance 3.21)** The company agree with the committee's conclusion that the increment approach to caregiver QALYs is appropriate. However, as stated in response to the first draft guidance consultation, the company would like to highlight that the EQ-5D utilities used in the analysis, while aligned to the NICE reference case, are insensitive and likely to underestimate the effect of AD and lecanemab on caregivers. Evidence from Reed et al. (2017) suggests EQ-5D-5L may be a suboptimal measure of the QoL of carers of people with AD, due to its focus on physical health.[17] The Zarit Burden Interview (ZBI) is a more appropriate tool for assessing carer QoL in AD than EQ-5D as it focused specifically on assessing caregiver burden. Results from Clarity AD, the only Phase 3 study of monoclonal antibodies for AD to collect HRQoL data, highlight the insensitivity of the EQ-5D. At 18 months, the ZBI showed a statistically significant 38.5% lower decline for caregivers of patients treated with lecanemab compared to placebo. In contrast, the EQ-5D showed only an approximately 10% mean difference versus placebo, with minimal decline at 12 months but a greater, non-significant decline ([redacted]% more than placebo) at 18 months for caregivers of patients treated with lecanemab. Notably, in the MMRM analysis, this translates to a small difference in health state carer utility of [redacted] between the MCI ([redacted]) and severe AD ([redacted]) health states.

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	A comparison of EQ-5D-5L, EQ visual analogue scale (VAS) and ZBI in the intention-to-treat (ITT) population is provided in Appendix A.2.2. EQ-5D-5L domain values indicate almost identical scores for MCI and mild AD, while EQ VAS values show a [redacted]% difference between the MCI and mild AD health states for lecanemab ([redacted]point difference on a 100-point scale). By contrast, ZBI scores show a [redacted]% difference between the MCI and mild AD health states for lecanemab ([redacted] difference on a 88-point scale). The minimal difference in caregiver QoL between health states for EQ-5D demonstrates that EQ-5D does not sufficiently capture changes in caregiver HRQoL and impacts cost-effectiveness of lecanemab. However, no validated algorithm exists to cross-walk ZBI to EQ-5D, therefore it was not possible to obtain caregiver utility values based on ZBI scores. The company note that the utility values used by the company in NICE ID6222, derived from a vignette study providing spouse and child caregiver utility values by health state for community and residential care settings, showed a substantial difference in caregiver utility between the MCI and severe AD health states. In the community setting, differences of 0.44 and 0.38 were observed for spouse and child caregivers, respectively. As these utility values appear to better reflect the impact of AD on caregivers, the company has explored these utility values in scenario analyses to reflect a more clinically plausible decline in caregiver utility between MCI and severe AD. The differences in utility between MCI and other health states from ID6222 were applied to the MCI health state caregiver utility from Clarity AD (Appendix A.2.4.2.3, Table 12) to maintain consistency with the utility values used for MCI in Clarity AD. A weighted average of spouse and child caregiver utility values in the community setting was used based on a ratio of the 1.8 caregivers in the model, weighted assuming 1.0 spouse and 0.8 child. Additionally, to address the committee's uncertainty regarding the differences in caregiver utility between community and institutional care, the approach assumes no additional disutility for patients in residential care. When applying this scenario, the reduction in utility value between the MCI and mild AD health states is 0.08, aligning closely to the percentage differences observed in the Clarity AD ITT ZBI data. This scenario analysis using the ID6222 company caregiver utilities as described above yields an ICER of £19,039, indicating vastly improved cost-effectiveness and highlighting the importance of appropriate utility measurement for caregivers. Further scenarios were explored combining the use of the ID6222 company caregiver utilities with the use of: the micro-costing estimate inclusive of overheads for chair time and the SB12Z HRG code, respectively. These scenarios yield ICERs of £19,529 and £22,349, respectively, further demonstrating the plausible cost-effectiveness of lecanemab.
9	**APOE4 testing costs (draft guidance 3.23)** Having reviewed the committee's preferred assumptions, the company is concerned that the committee's plausible lower bound would not reflect the uncertainty in APOE4 testing costs and is therefore not reflective of the true lower bound ICER. The APOE4 testing costs used in the model (comprised of the APOE4 test unit cost, one outpatient appointment, and genetic counselling costs) were previously aligned with cost estimates from the NHSE BIA submission, in absence of alternative costs. However, the company were unable to verify these costs, and it is therefore unclear whether they are reflective of the true costs of APOE4 testing. The company note that the testing unit cost of £41.10, as per Scottish Health Service costs, R130 Laboratory Services, Clinical Genetics, is substantially lower than the testing unit cost assumed by NHSE. As the only verifiable UK-based APOE4 testing cost available, the company have adopted this in the revised base case (Appendix A.2.3, Table 7). A scenario analysis exploring the NHSE BIA submission cost for APOE test unit cost indicates this has a small impact on the ICER (£30,013 in the base case).

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10	**Managed access (draft guidance 3.26)** [redacted][18]

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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ACD response – appendix

April 2025

File name	Version	Contains confidential information	Date
[ID4043]_Lecanemab_ACD_appendix_4Apr2025_CON_FINAL	1.0	Y	4th April 2025

A.1 Clinical data

A.1.1 Amyloid beta

Mean amyloid PET levels observed in Clarity AD in the licensed population for patients discontinuing treatment after 3, 6, 12 and 18 months are presented in Table 1.[1] A summary of the treatment waning assumptions applied in the revised base case is presented in Table 2**Error! Reference source not found.**.

Table 1: Mean amyloid PET levels - Clarity AD, modified population

	Time on treatment (months)				
	Baseline	**3**	**6**	**12**	**18**
Mean amyloid levels (CL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients discontinuing	-	[redacted]	[redacted]	[redacted]	[redacted]
Pooled mean amyloid levels (CL) at discontinuation	-	[redacted]			[redacted]

Abbreviations: AD – Alzheimer's disease; CL – Centiloid; PET – positron emission tomography
Source: Clarity AD CSR (APOE4 non-carriers and heterozygous carriers)[1]

Table 2: Summary of waning assumptions

		Base case		Scenario #4*	
Discontinuation time point	**Waning start**	**Waning duration**	**Total waning period**	**Waning duration**	**Total waning period**
Definition	Time to reach 30 CL	Time to reach 50 CL	-	Time to reach baseline ([redacted])	-
Pre-18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*See comment 4 for details.
Abbreviations: CL – Centiloid
Source: Clarity AD CSR[1] - Derived from
Table 1 assuming 2.6 CL per year re-accumulation rate.

A.1.2 Treatment discontinuation

The time-to-treatment discontinuation graph for the modified population in Clarity AD is presented in Figure 1.[1]

Figure 1: Time-to-treatment discontinuation - Clarity AD, modified population

Source: Clarity AD CSR (APOE4 non-carriers and heterozygous carriers)[1]

A.2 Economic data

A.2.1 Micro-costing exercise

The micro-costing exercise, shared in response to the first draft guidance consultation, estimated a cost of £139.12 for the administration of lecanemab; this accounted for an average of 30.8 minutes of active HCP time during the 60-minute infusion of lecanemab. As detailed in response to the second draft guidance, comment 3, the company have included a scenario analysis using an updated micro-costing estimate to include the cost of overheads for the remainder of the 60 minutes not associated with active HCP time (29.2 minutes). This cost was calculated using the proportion of the PSSRU unit cost for a band 5 nurse associated with overheads and capital overheads.[2]

The updated infusion cost estimated by the micro-costing exercise is £149.26. A summary of the revised HCP time calculations is presented in Table 3, with updates in bold. The cost associated with drug preparation remains as per the original micro-costing exercise described in response to the first draft guidance. Table 4 summarises the inputs used to calculate an overheads cost of £20.86 per hour associated with HCP-inactive chair time, yielding an additional £10.15 to the micro-costing estimate.

Table 3: Micro-costing HCP time and resource use

Task	HCP time (minutes)					PSSRU resource			
	HCP1	**HCP2**	**HCP3***	**HCP4**	**Average time**	**HCP1**	**HCP2**	**HCP3***	**HCP4**
Pre-infusion set up	8.6	10	-	9.3	9.3	Healthcare Assistant (Band 3/4)	Nurse (Band 5+)	-	Nurse (Band 5+)
Drug preparation	As per original micro-costing exercise								
Drug collection and check	10	17.5	-	13.75	13.75	Infusion suite nurse (Band 5) + second nurse to check (Study nurse Band 6)	Nurse (Band 5+) + second nurse to check (Band 5+)	-	Nurse (Band 5+) + second nurse to check (Band 5+)
Pre-drug pt checks	-	15	-	5	10	-	Nurse (Band 5+)	-	Nurse (Band 5+)
Drug administration	10	7.5	-	60	25.8	-	Nurse (Band 5+)	-	Nurse (Band 5+)
Patient monitoring during administration	2.5	7.5	-	5	5	-	Nurse (Band 5+)	-	Nurse (Band 5+)
HCP-inactive chair time	29.2**					**Nurse (Band 5) overheads only**			
Saline flush	1.5	8.5	-	5	5	-	Nurse (Band 5+)	-	Nurse (Band 5+)
Remove and discard IV	1.6	1.6	-	1.6	1.6	-	Nurse (Band 5+)	-	Nurse (Band 5+)
Patient monitoring post-administration	60	10	-	35	35	-	Nurse (Band 5+)	-	Nurse (Band 5+)
Discharge patient	1.8	0	-	5	2.3	-	Nurse (Band 5+)	-	Nurse (Band 5+)
Total HCP active time (minutes)	96	77.6	-	139.65	107.8	-	-	-	-
Total (hours)	1.60	1.29	-	2.33	1.80	-	-	-	-

*As HCP3 is a pharmacist, they did not provide comments on the timing and resource use of these tasks. **Calculated as 60 minutes for the infusion of lecanemab minus 30.8 minutes of active HCP time (25.8 minutes for drug administration and 5 minutes for patient monitoring during administration)
Abbreviations: HCP – healthcare professional; IV – intravenous; PSSRU – Personal Social Services Research Unit

Table 4: PSSRU cost inputs for overheads associated with band 5 nurse

PSSRU HCP	Cost per working hour (£)	Source
Overheads: Management, admin and estates staff	6.14	Band 5 nurse, PSSRU 2023 (pg 91) total of non-salary related costs divided by total working hours per year (1,496)
Overheads: Non-staff	8.74	
Capital overheads	5.98	
Total hourly cost, overheads only	20.86	

Abbreviations: HCP – healthcare professional; PSSRU – Personal Social Services Research Unit.

A.2.2 Caregiver utilities

As detailed in response to the second draft guidance, comment 8, the EuroQol 5-Dimension (EQ-5D) scale is insensitive to changes in caregiver health-related quality of life (HRQoL) associated with decline in health for the patient they care for, and likely to underestimate the impact of AD and lecanemab on caregivers. A summary of baseline values in EQ-5D-5L by domain, EQ visual analogue scale (VAS) and Zarit Burden Interview (ZBI) for caregivers by health state for MCI and mild AD is shown in Table 5 and Table 6, respectively.

Table 5: Summary of baseline values in EQ-5D-5L (ITT population)

Baseline, mean (SD)	MCI due to AD		Mild AD	
	Lecanemab (n=528)	Placebo (n=544)	Lecanemab (n=331)	Placebo (n=331)
Mobility	[redacted]	[redacted]	[redacted]	[redacted]
Self-care	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	[redacted]	[redacted]	[redacted]	[redacted]
Pain/discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/depression	[redacted]	[redacted]	[redacted]	[redacted]
Health today (VAS)	[redacted]	[redacted]	[redacted]	[redacted]

Health states for this analysis are defined by the NIA-AA clinical diagnosis not CDR-SB
Abbreviations: AD – Alzheimer's disease; ITT – intention-to-treat; MCI – mild cognitive impairment; SD – standard deviation; VAS – visual analogue scale
Source: Clarity AD CSR, Table 14.2.3.4.1all - Summary of Change from Baseline in EQ-5D-5L by Visit[1]

Table 6: Summary of baseline scores in ZBI of caregiver (ITT population)

Baseline, mean (SD)	MCI due to AD		Mild AD	
	Lecanemab (n=528)	Placebo (n=544)	Lecanemab (n=331)	Placebo (n=331)
Total score	[redacted]	[redacted]	[redacted]	[redacted]

Health states for this analysis are defined by the NIA-AA clinical diagnosis not CDR-SB
Abbreviations: AD – Alzheimer's disease; ITT – intention-to-treat; MCI – mild cognitive impairment; SD – standard deviation; ZBI – Zarit's burden interview
Source: Clarity AD CSR, Table 14.2.3.6.1all - Summary of Change from Baseline in Zarit's Burden Interview of Study Partner by Visit[1]

A.2.3 Updated model inputs

As detailed in the draft guidance response, comment 1, the cost-effectiveness model inputs have been updated to address remaining uncertainties by aligning with committee preferred assumptions, or the concurrent appraisal of donanemab for MCI and mild dementia caused by AD (NICE ID6222), where these reduce or resolve uncertainty or better reflect current UK practice. The inputs changed, their values, sources, and reference in the draft guidance response are presented in Table 7.

Table 7: Updated cost-effectiveness model inputs (base case)

Variable			Value or reference to appropriate section in draft guidance response or CEM	Source
Clinical inputs	Baseline characteristics	Proportion MCI due to AD	20.4%	Donanemab second draft guidance, TRAILBLAZER-ALZ2 trial[3,4]
		Proportion mild AD	79.6%	
	Treatment waning	Waning for all off-treatment health states, regardless of reason for discontinuation	Draft guidance response comment 4; 'Engine_Lec' sheet in CEM	Amyloid re-accumulation analysis, Eisai data on file
	Mortality	General population mortality for MCI (HR=1)	'Clinical data' sheet in CEM	Committee preference[5]
Utility data	Patient	Patient-reported EQ-5D for MCI and mild AD health states	Draft guidance response comment 7	Clarity AD MMRM, Eisai data on file[1]
	Caregiver	Number of caregivers per patient	1.8	Donanemab second draft guidance, GERAS study[3,6]
Cost inputs	Health state	Wittenberg et al. 2019 health state costs avoiding assumption on the proportion of non-medical costs attributable to private care	'Cost data' sheet in CEM	Donanemab second draft guidance, Wittenberg et al. (2019)[3,7]
	APOE4 testing costs	Scottish Health Service APOE4 testing cost	'Cost data' sheet in CEM	Public Health Scotland 2022/23. R130 report[8]

Abbreviations: AD – Alzheimer's disease; APOE4 – Apolipoprotein E4; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating – Sum of Boxes; CEM – cost-effectiveness model; EQ-5D-5L – EuroQol 5-Dimension

5-Level; kg – kilogram; MCI – mild cognitive impairment; MMRM – mixed model for repeated measures; MSM – multistate model; NHSE – National Health Service England.

A.2.4 Cost-effectiveness results

A.2.4.1 Updated base case results

Based on a [redacted] for lecanemab, the cost-effectiveness of lecanemab compared with SoC is £29,706 per QALY gained (Table 8).

Table 8: Base case results

Technologies	Total			Incremental			ICER (per QALY)	NHB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,706	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]					

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care.

A.2.4.1.1 Cumulative ICER impact of base case updates

As outlined in the draft guidance response, several updates have been made to the cost-effectiveness model base case; details of each change are provided in comment 1. The cost-effectiveness results after cumulatively applying each change are presented in Table 9.

Table 9: Updated base case cost-effectiveness results (PAS price)

#	Assumption	ICER (change vs previous row)	ICER (cumulative change)
Previous company base case (as per first draft guidance response 23rd September 2024)		£39,525	
1	Revised simple PAS ([redacted]%)	[redacted]	[redacted]
2	Baseline distributions of patients across MCI and mild AD health states amended to better reflect UK practice, in line with ID6222 committee preference	[redacted]	[redacted]
3	Number of caregivers per patient (1.8) as a multiplication factor to the caregiver utilities, in line with ID6222 committee preference	[redacted]	[redacted]
4	Use of the health state costs from Wittenberg et al. 2019 in line with ID6222 committee preference	[redacted]	[redacted]
5	Applying treatment waning to all off-treatment health states	[redacted]	[redacted]

#	Assumption	ICER (change vs previous row)	ICER (cumulative change)
6	Use of patient-reported EQ-5D for MCI and mild dementia health states in line with committee preference	[redacted]	[redacted]
7	Use of general population mortality for MCI (HR=1) in line with committee preference	[redacted]	[redacted]
8	Scottish Health Service APOE4 test unit cost	[redacted]	[redacted]
Updated company base case		**£29,706**	

Abbreviations: ICER – Incremental cost-effectiveness ratio; PAS – Patient Access Scheme; SoC – standard of care

A.2.4.2 Sensitivity analyses results

A.2.4.2.1 Probabilistic sensitivity analysis (base case only)

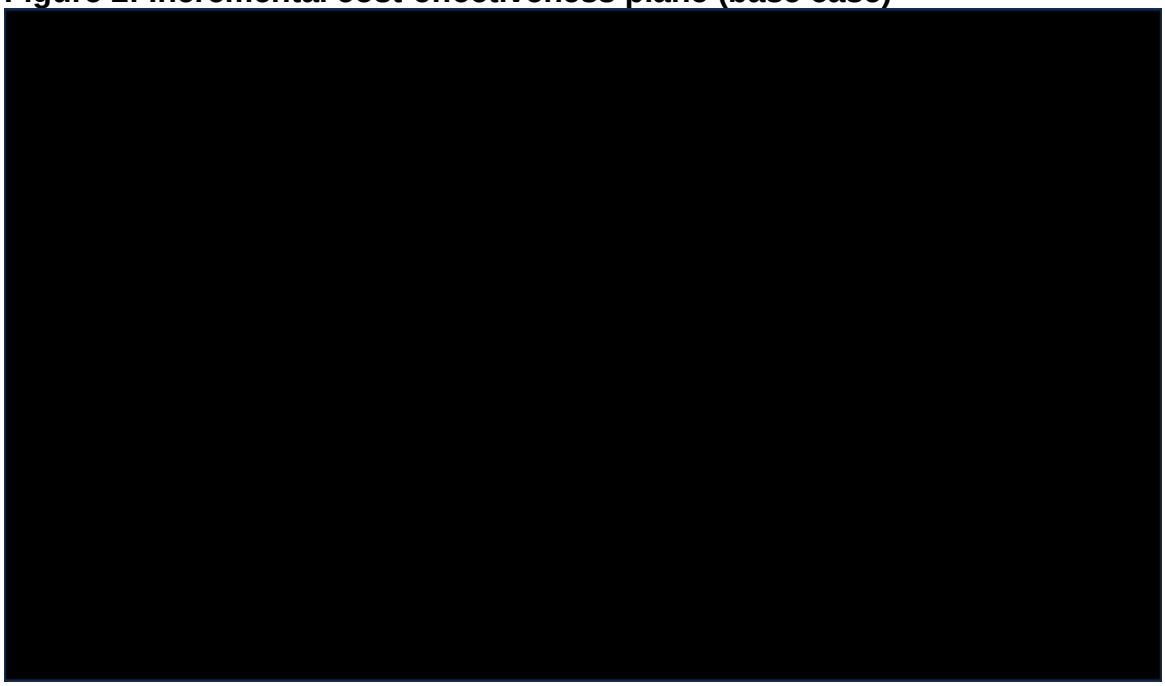
The mean costs and QALYs in the probabilistic sensitivity analysis were comparable to the deterministic base case values, resulting in a probabilistic ICER £202 higher than the base case ICER (£29,908/QALY, Table 10), a 0.68% difference from the deterministic ICER. The incremental cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 2 and Figure 3, respectively.

Table 10: PSA results (base case)

Technology	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (per QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£29,908
Lecanemab	[redacted]	[redacted]			

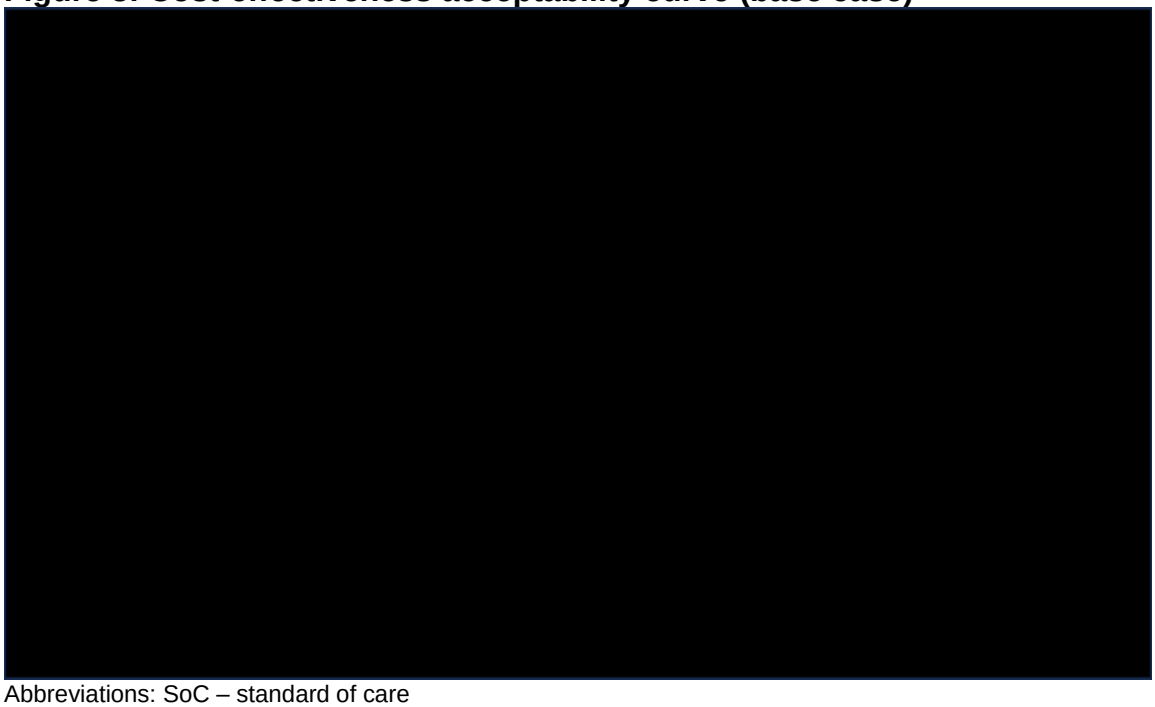
Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SoC – standard-of care

Figure 2: Incremental cost-effectiveness plane (base case)



Abbreviations: SoC – standard of care; QALY – quality-adjusted life year.

Figure 3: Cost-effectiveness acceptability curve (base case)



Abbreviations: SoC – standard of care

A.2.4.2.2 One-way sensitivity analyses (base case only)

A one-way sensitivity analysis (OWSA) tornado diagram presenting the top ten most sensitive parameters is presented in Figure 4 with tabulated results presented in Table 11.

Table 11: Tabulated OWSA results for lecanemab vs SoC (base case)

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Time to worsening HR, mild AD (CDR-SB)	£23,250	£50,696	£27,446
Utility: Farina (carer as proxy) - Mild AD	£44,307	£25,430	£18,877
Time to worsening HR, MCI due to AD (CDR-SB)	£24,201	£38,133	£13,931
Utility: Farina (carer as proxy) - Severe AD	£25,647	£38,712	£13,064
Lecanemab compliance	£24,984	£34,428	£9,444
Farina caregiver institution decrement	£35,803	£28,110	£7,693
Utility: Farina (carer as proxy) - Moderate AD	£27,444	£32,374	£4,930
Caregiver utility: Black - community - Severe AD	£32,330	£27,476	£4,854
Caregiver utility: Black - community - Moderate AD	£32,774	£28,198	£4,576
Lecanemab cost of administration (micro-costing)	£27,607	£31,805	£4,197

Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis; SoC – standard of care.

Figure 4: OWSA tornado diagram (base case)

Abbreviations: AD - Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR – hazard ratio; ICER – incremental cost-effectiveness ratio; MCI – mild cognitive impairment.

A.2.4.2.3 Scenario analyses

Scenario analysis results are presented in Table 12.

Table 12: Scenario analysis results (base case)

#	Scenario	ICER
	Base case	**£29,706**
1.	Inclusion of micro-costing infusion cost for lecanemab administration with overheads associated with chair time	£30,471
2.	Inclusion of the chemotherapy SB12Z HRG code for lecanemab infusion	£34,870
3.	Treatment effect waning for all off-treatment states based on time to return to baseline amyloid PET level ([redacted])	£26,547
4.	Assume [redacted] for all off-treatment moderate to severe AD patients, 75% treatment effect for other off-treatment health states (EAG preference)	£28,614
5.	Assuming a proportion (10%) of patients remain on treatment following permanent move to institutional care	£30,225
6.	Include six-monthly outpatient appointments	£30,995
7.	Use of patient-by-proxy EQ-5D utility values for MCI and mild AD	£29,383
8.	NICE ID6222 company caregiver utility values and removal of caregiver disutility on institution	£19,039
9.	Scenario 8 plus scenario 1 (micro-costing infusion cost with overheads associated with chair time)	£19,529
10.	Scenario 8 plus scenario 2 (SB12Z HRG code infusion cost)	£22,349
11.	Removal of caregiver disutility on institution	£34,056
12.	Inclusion of the NHSE APOE4 test unit cost	£30,013

Abbreviations: AD – Alzheimer's Disease; CDR – Clinical dementia rating; CL – centiloid; EAG – external assessment group; HR – hazard ratio; HRG – healthcare resource group; ICER – incremental cost-effectiveness ratio; MCI – mild cognitive impairment; MRI – magnetic resonance imaging; NHSE – National Health Service England; NICE – National Institute for Health and Care Excellence.

A.2.4.3 Disaggregated results (base case)

Disaggregated results are presented in Table 13.

Table 13: Disaggregated QALYs and LYs (base case)

Treatment status	Setting	Health state	Discounted			Undiscounted		
			SoC	Lecanemab	Incremental vs. SoC	SoC	Lecanemab	Incremental vs. SoC
QALYs								
On-treatment	Community	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Institution	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment	Community	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Institution	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life years								
On-treatment	Community	MCI due to AD	-	-	-	[redacted]	[redacted]	[redacted]
		Mild AD	-	-	-	[redacted]	[redacted]	[redacted]

Treatment status	Setting	Health state	Discounted			Undiscounted		
			SoC	Lecanemab	Incremental vs. SoC	SoC	Lecanemab	Incremental vs. SoC
		Moderate AD	-	-	-	[redacted]	[redacted]	[redacted]
		Severe AD	-	-	-	[redacted]	[redacted]	[redacted]
	Institution	MCI due to AD	-	-	-	[redacted]	[redacted]	[redacted]
		Mild AD	-	-	-	[redacted]	[redacted]	[redacted]
		Moderate AD	-	-	-	[redacted]	[redacted]	[redacted]
		Severe AD	-	-	-	[redacted]	[redacted]	[redacted]
Off-treatment	Community	MCI due to AD	-	-	-	[redacted]	[redacted]	[redacted]
		Mild AD	-	-	-	[redacted]	[redacted]	[redacted]
		Moderate AD	-	-	-	[redacted]	[redacted]	[redacted]
		Severe AD	-	-	-	[redacted]	[redacted]	[redacted]
	Institution	MCI due to AD	-	-	-	[redacted]	[redacted]	[redacted]
		Mild AD	-	-	-	[redacted]	[redacted]	[redacted]
		Moderate AD	-	-	-	[redacted]	[redacted]	[redacted]
		Severe AD	-	-	-	[redacted]	[redacted]	[redacted]
Costs								
On-treatment	Community	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Institution	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment	Community	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment status	Setting	Health state	Discounted			Undiscounted		
			SoC	Lecanemab	Incremental vs. SoC	SoC	Lecanemab	Incremental vs. SoC
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Institution	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's Disease; LY – life years; MCI – mild cognitive impairment; QALY – quality-adjusted life year; SoC – standard of care.

A.3 References

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Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

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Consultation on the draft guidance document – deadline for comments **5pm** on **Thursday 27 March 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alzheimer's Research UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**We agree with the committee that there remains significant uncertainty surrounding infusion costs**. Notably, there is still a significant discrepancy between the company's cost estimate of £208 and NHS England's figure of £432 (previously £565). We would once again like to highlight estimates we obtained from clinicians regarding real-world infusion costs:

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	1. One clinician estimated the cost to be between £300 and £400 per hour of infusion. 2. Another clinician observed that £500 might be high but acknowledged it could reflect broader administrative and operational considerations. 3. A third clinician estimated that a 1-1.5-hour infusion would likely cost around £250 to £300, considering nurse time, overheads, and some clinician time. These estimates indicate that the real-world cost of infusion is uncertain and most likely lies somewhere between NHS England and company estimations. We believe **the committee should consider a managed access scheme** as this would allow uncertainties, such as infusion costs, to be clarified from real-world usage.
2	NICE, NHS England, and the company should **continue exploring the possibility of a managed access scheme** for lecanemab. The innovative nature of lecanemab means there are several uncertainties surrounding its real-world use. A managed access scheme would allow many of these questions to be answered as well as providing a range of benefits for dementia patients and the wider healthcare system. Managed access has the potential to: • Help determine the overall cost of treatment in a real-world NHS setting, including infusion costs. • Give a greater insight into the long-term efficacy of the treatments in a real-world population rather than a trial population. • Gain a greater understanding of the impact of lecanemab treatment on patient and carer quality of life, an aspect of the current evaluation which the committee notes there remains uncertainty. • Meaningful insights for research in Alzheimer's disease. • Help prepare the healthcare system for wider deployment of treatments in the pipeline. • Improve the lives of those affected by the disease. Concerns over barriers to both implementation and data collection in the NHS should not prevent data collection efforts. While there may be challenges, including the lack of existing infrastructure or registries for Alzheimer's disease, these obstacles must be addressed proactively rather than delaying or halting real-world data collection altogether. Although we appreciate that resolving these issues is out of scope for a single technology appraisal, we believe that proactively addressing these obstacles through a managed access scheme will present a range of benefits. These include ensuring system readiness for future treatments in the pipeline and overall improvements in clinical care provided for dementia patients in the NHS.
3	We feel **the true impact on carers' quality of life is not being incorporated** in the evaluation process. Although this aspect is mentioned in the guidance papers, the committee note there remains significant uncertainty around the impact on carer quality of life. We know the EQ-5D is generally used as a measure of quality of life in this area and we would like to understand the criteria NICE used to assess how appropriate a measure this is in reflecting the impact on carers for Alzheimer's disease patients.
4	Estimated at £21.1bn per year,[i] **the bulk of the cost of dementia care falls on unpaid carers** rather than in healthcare (£7.1bn per year), and we feel that by not including the financial and productivity impact on carers of Alzheimer's patients in the evaluation, **the significant cost of informal care is being neglected**. While lecanemab may not currently be deemed cost-effective due to other factors, considering informal care costs could have a

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	substantial impact on the ICER. A thorough assessment of the treatment's value should consider that dementia costs are largely borne by individuals and families rather than the state. Given these factors, we would like to understand **if there is potential to apply a non-reference case to more accurately reflect these significant costs**. We also believe there would be **value in a managed access scheme** as this would allow the social and economic benefits that carers experience in a real-world setting to be captured. The committee would subsequently be able to make a more informed assessment on the economic impact unpaid care in the evaluation process.
5	We are concerned that lecanemab is **not eligible for the severity modifier**, despite Alzheimer's being the leading cause of death in the UK and imposing a significant disease burden. There is a clear clinical consensus that treating Alzheimer's in its milder stages is more beneficial than addressing it in later stages when care needs are much higher. However, lecanemab is excluded from the severity modifier due to the age of the population and the chronic nature of the disease, which overlooks the condition's impact and the value of extending time in milder stages. We believe this approach needs reconsideration. We are aware of broader concerns about the severity modifier's role in limiting access to innovative treatments, as recently highlighted by the ABPI.[ii] [iii] We believe that the challenges posed by diseases like Alzheimer's should be considered, and the scope of the severity modifier should be expanded to better address such conditions in the future.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

[i] Alzheimer's Society and Carnall Farrar. The economic impact of dementia, Module 1, 2024. https://www.alzheimers.org.uk/sites/default/files/2024-05/the-annual-costs-of-dementia.pdf

[ii] https://www.abpi.org.uk/media/blogs/2024/august/understanding-medicines-access-a-look-at-the-severity-modifier-and-its-impact/

[iii] https://www.abpi.org.uk/media/rf1phcti/abpi-connie-2-report-august-2024.pdf

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alzheimer's Society

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Alzheimer's Society welcomes NICE's appraisal of lecanemab, the first disease-modifying treatment to be appraised by UK regulators, as an important milestone for dementia. We respect this second draft recommendation from NICE, whilst also recognising the disappointment that

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	many people will have experienced on learning the decision. We accept NICE's assessment that the cost-effectiveness estimates for lecanemab are uncertain but are above NICE's cost effectiveness threshold.
2	We welcome NICE holding a second draft guidance consultation and a third committee discussion to give further consideration to remaining issues. We appreciate the rigour and flexibility demonstrated by NICE in their appraisals of the first disease-modifying treatments for Alzheimer's disease. We hope that learnings from this process will inform appraisals of future treatments.
3	We would also encourage NICE to monitor and review real-world data on the benefits and risks of lecanemab, as well as data from any ongoing clinical trials.
4	We have no new evidence to submit further to our original evidence submission to the appraisal and our response to the consultation on the first draft guidance.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	Differences in the cost-effectiveness modelling produced by the company and the evidence advisory group are expected, but we note that this discrepancy is at least 3-4 times higher using the EAG's calculations (base case ~£105K) than those estimated by the company (base case ~£39K) While some of the sources of these differences are redacted, factors influencing treatment-effect estimates include the proportions of individuals with MCI-AD and mild AD-dementia, health-related QoL of patients and carers, infusion costs, and stopping criteria. These are addressed in turn below.
2	Proportions of patients with MCI-AD and mild AD We note that there is no existing NICE guidance on the diagnosis of management of MCI. The best real world data to indicate the likely proportion of MCI-AD versus mild-AD probably comes from the 2023 national audit of memory services : mas-2023-appendices-ii-v.pdf In this cohort of all patients seen in memory service, 17% were diagnosed with MCI, compared with 71% who had any type of dementia. (This is not specific to Alzheimer pathology but gives a useful indication of the ratio of MCI to mild dementia. 42% of cases of dementia were thought to be due to Alzheimer pathology. There is no estimate of what proportion of MCI is due to Alzheimer pathology but we might assume that this would be similar). In 2019, the figures were 17% for MCI and 67% for dementia, so there does not seem to be a trend for patients to present at an earlier stage over time. However, many neurologists believe that there will be a shift to earlier presentation as public awareness of potential disease modifying treatments grows.
3	Diagnostic costs Most neurologists believe that CSF biomarkers should be considered part of the "standard of care" in the diagnosis of dementia. However, we note thatCSF biomarkers are only recommended by NICE if the diagnosis can't be made using clinical assessment and brain scan (amyloid PET is not recommended) and that biomarkers are not routinely offered in memory services. Although a blood test for AD pathology (p-tau217) is now available in an UKAS approved lab (https://www.uclh.nhs.uk/our-services/find-service/neurology-and-neurosurgery/neuroimmunology), it is not currently recommended by the manufacturer as a test for determining treatment eligibility. It may have potential to screen out individuals below the lower cut-point, but those with indeterminate or positive results would still need CSF examination or PET. It is unclear whether using blood biomarkers in the whole population to reduce CSF/PET use would be cost-saving overall. Further research on the real world use of blood based biomarkers in a UK memory clinic population would be useful We agree that the cost of ApoE genotyping should be considered part of the cost of treatment.
4	Health related QoL We are concerned about the face validity of using carer utility values which are virtually identical in MCI, mild AD, and moderate AD. By definition patients with MCI have normal activities of daily living, whereas those with dementia need assistance. Anyone living with dementia or caring for patients and caregivers with dementia will attest to the increased burden on carers as dementia starts and progresses.
6	Stopping criteria. We do not believe that this will be overly onerous to operationalise. All patients receiving treatment will receive follow-up (although we note that this represents a change from current care in Alzheimer's disease, where most patients are not offered routine follow-up). We note that it can

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	be hard for clinicians to stop a medication if patients or families perceive it to be causing benefit or providing hope, and this may impact on the real world implementation of stopping criteria.
7	We welcome the committee's opinion that there is a high likelihood that a managed access programme within the NHS has the potential to provide invaluable information about implementation of these new therapies in a real-world setting, which is simply impossible in the (necessarily) artificial setting of a clinical trial. We feel that a managed access programme could not only provide important information regarding the cost-effectiveness of this drug but will also help the NHS prepare for the delivery of disease-modifying therapies for the dementias moving forward.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Psychiatrists

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1	Under managed access - would administration costs be substantially reduced if the commercially available blood biomarkers are used as the primary biomarker to determine amyloid positivity / eligibility? Subject the MHRA approval, could this substantially reduce the need for lumbar punctures (for CSF biomarkers) or amyloid -PET and therefore costs and patient acceptability? **Comment:** There is growing evidence that blood-based biomarkers offer comparable performance to both CSF and amyloid-PET biomarkers, especially when using ultrasensitive methods of measurements (eg see references below).
2	Under managed access - would using an 18-month time-dependent discontinuation/stopping rule help to reduce overall costs? Would this provide a clearer prescribing pathway and address uncertainties about the duration of treatment otherwise based on the clinical appraisal of transitioning to moderate AD (which could be difficult to determine with the same level of consistency c/w a time dependent stopping rule)? **Comment:** 18 months is shorter than the MHRA licence but consistent with donanemab's licence and aligns with the data from the pivotal phase III lecanemab trial.
3	We are mindful that dementia that includes Alzheimer's disease carries a huge personal and societal burden, and continues to be the most common cause of death in the UK. Does this impact on decisions about the importance of managed access? **Comment:** Alzheimer's disease is a complex disease with multiple putative mechanisms and ultimately to move beyond current symptomatic treatments progress will be stepwise and most likely modest. There is a need for more accurate diagnostic and novel treatment pathways.
4	References: Barthélemy, N.R., Salvadó, G., Schindler, S.E. et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. Nat Med30, 1085–1095 (2024). Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024 Jun 27. doi: 10.1002/alz.13859. Schindler, S.E., Galasko, D., Pereira, A.C. et al. Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease. Nat Rev Neurol 20, 426–439 (2024a). https://doi.org/10.1038/s41582-024-00977-5 Schindler SE, Petersen KK, Saef B, et al. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. Alzheimer's Dement. 2024b; 20: 8074–8096

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Clinical Pharmacy Association (UKCPA) Neurosciences Committee

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1	The Committee acknowledge the relatively moderate level of gains compared to risk and burden and contemplates whether investment might be more beneficial if directed toward improving pathways and care for all, rather than solely for eligible patients.
2	The Committee reflected on the implication of genetic testing and feels the need of more clarification as well as care pathways that should include support for both patients and their families.
3	The Committee recognises the limitations of the population excluded from clinical trials (Down's syndrome, early onset dementia and some ethnic groups) but also acknowledge that clinical trials populations do not always reflect real-world diversity and lack of diversity in trials is a widespread issue across healthcare research.
4	The Committee recommends that the commissioning process should look at determining appropriate resource allocation across diagnosis, treatment, and cessation.
5	The Committee encourages real-world data collection through partnerships to allow pathway modifications if needed.
6	The Committee predicts a significant burden for the infusion unit due to one hour infusion every two weeks and recognise many infusion units are already at full capacity hence they may struggle to support the treatment, as well as outpatient capacity.
7	The Committee acknowledge that additional training might be necessary for neurology, psychiatry, and geriatric medicine clinics.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dementia Research Centre, UCL

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Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……
1	**Model starting proportions - proportions of patients with MCI-AD and mild AD:** it is likely in our view that awareness of disease-modifying treatments (on the NHS) will lead to individuals coming forward earlier to seek advice about cognitive complaints. It is our

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	experience in our Centre that individuals (and families) present later in the disease when they think there is little that can be done in terms of slowing progression. This is already changing and is likely to increase the proportion of people seeking advice at an MCI stage. The availability of blood tests (plasma ptau217 is now available) could speed up the time needed to determine amyloid positivity and eligibility – this would also increase the proportion who are at an MCI-AD stage (vs mild AD stage) compared to estimates derived from current memory service surveys/data. A managed access scheme may well also use a fast track screening approach to reduce the time to diagnosis for those who might be eligible.
2	We are very concerned about the utility values being used – especially for carers. The EQ-5D scores derived from the GERAS study (Reed et al) appear very far from my experience as a clinician having discussed with many carers their concerns and distress and burden when caring for someone with dementia. Three of the 5 domains in the EQ-5D: mobility, self-care, and usual activities have little bearing on what the carers of my patients describe as the impact of caring. = I have discussed with carers how they feel their quality of life has been affected by their life partner / spouse having mild dementia or severe dementia – these are consistently much lower than the numbers presented at the meeting (derived from the Reed et al paper) 0.86 falling to 0.75. As a result, I conducted a questionnaire based (SLIDO) survey of attendees at the Alzheimer's Research UK Conference (March 2025) ~250 people responded (all answers were independently provided). I described what constituted a CDR score of 1 (mild dementia) and a CDR score of 3 (severe dementia). Participants were then asked a series of questions which included asking them to rate what they would estimate *their* quality of life to be if their partner/spouse (who they lived with) had MILD dementia – and then a similar question for *their* quality of life if their spouse/partner had SEVERE dementia - (on a 0 to 100 scale, where 100 is perfect health): Mean QoL rating for having a partner with **mild** dementia was 57.5 (or **0.58** on a 0-1 scale) (n=254) Mean QoL rating for a partner with **severe** dementia was 26.9 (or **0.27** on a 0-1 scale) Participants were also to rate what they would imagine their own quality of life to be with mild or with severe dementia Mean QoL rating for *themselves* having **mild** dementia was 50.8 (or **0.51** on a 0-1 scale) (n=250) Mean QoL rating for *themselves* having **severe** dementia was 8.2 (or **0.08** on a 0-1 scale) These are unpublished results (manuscript in preparation) but they accord with my clinical experience of how much impact there is of caring for someone with severe dementia.
3	Carers: it is worth noting that most people that would choose and be eligible to start treatment would very likely have someone (partner/ care-giver) living with them – almost a pre-requisite for treatment (iv infusions etc) – i.e. a minimum of one carer who will experience the impact of living with and caring for that person with dementia.
4	
5	
6	

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Infusion Cost Estimates

Introduction

As part of the Health Technology Appraisals (HTAs) for donanemab and lecanemab, NHS England provided an estimate of the unit price for the administration of an infusion of a monoclonal antibody likely to be charged through the NHS Payment Scheme[1]. The NHS Payment Scheme defines the "rules to establish the amount payable for NHS-funded secondary healthcare."

NHS England is conscious that, as a material element of treatment costs, infusion pricing is an important consideration for the committee. Based on the supporting analysis summarised in this note, NHS England remains confident that its submitted estimate remains at the lower end of estimates of the price that would be paid by ICBs in a routine commissioning scenario.

Setting a price for monoclonal antibody infusion in Alzheimer's Disease or Dementia

As set out in previous notes, there is no Health Resource Group (HRG) code that covers a monoclonal antibody infusion to treat Alzheimer's Disease or Dementia currently in use. It is standard policy only to set a HRG price for a new area of activity up to three years after the activity starts in order for there to be sufficient reference data on which to base the price. Before then, it is normal to agree a price to be paid by commissioners (in this case ICBs) to NHS providers, using an estimate based on similar types of activity.

The methodology for estimating the average price for an infusion of a monoclonal antibody in the treatment of Alzheimer's disease, as submitted to NICE was as follows

Step 1	For each financial year (FY), define activity using
	• x292 Continuous intravenous infusion of therapeutic substance in combination with:
	  ○ x891 monoclonal antibodies band 1
	  ○ x892 monoclonal antibodies band 2

Step 2	Extract data from secondary user services dataset for • Admitted Patient Care (APC[2]) for both elective and day case • Outpatient attendance
Step 3	Remove non-elective zero price HRG activity (this where the system is used locally to record activity, but prices are not recorded accurately)

[1] NHS England » NHS Payment Scheme

[2] APC covers both elective admitted episode and day case. For the estimate both have been included due to inconsistent use of coding by NHS Providers. For elective episodes, spell has been limited to length of stay of zero or one to remove non-relevant episodes of care

Step 4	Limit Admitted Patient Care (APC) elective spells length of stay to zero or 1
Step 5	Calculate average price and uplift in line with NHS tariff inflation
Step 6	Apply average market forces factor (MFF)
	Point to note about NHS Payment Scheme: NHS tariff prices are used by commissioners to pay NHS providers for patient activity. This price covers the immediate cost of the appointment or procedure in terms of staff costs and consumables, plus an appropriate share of estates, patient transport costs, energy costs, training and other overhead costs. Medicine costs for the cost of monoclonal antibodies or other High Cost Drugs are explicitly excluded. It is therefore important, from a costing perspective, that other representations on price made to the committee consider the incorporation of equivalent elements.

The SQL code for this query can be found in the "SQL code" tab of the accompanying spreadsheet

The query estimate gives an average price of £361 from 227 episodes in financial year 2021/22. This is shown in table 1 below, along with, for completeness, values for other financial years.

Table 1: Output of price estimate query by financial year using codes x292 in combination with x891 or 892

Financial Year	Count	Total_Tariff_Initial_Amount	Average price
2018/19	320	155,427	486
2019/20	525	187,727	358
2020/21	63	23,139	367
2021/22	227	81,887	361
2022/23	195	75,546	387
2023/24	212	85,213	402

Adjusting the price to reflect advice from the pricing team that the resource for this type of infusion can be considered as similar to COVID MABs, and also in line with inflation, efficiencies, and an average Market Force Factor, gives a price estimate of £462[3].

[3] See "Inflation, efficiency, MFF" tab of accompanying spreadsheet for respective uplift factors

Re-running the estimate using data from 2023/24 gives a price estimate of £402 for 2023/24. Uplifting as above for inflation, efficiencies and average MFF gives a figure of £444. Applying the COVID resource factor would give a value of £489.

During the review of the price estimate, we noted that the volume of spells used to estimate the average price, at 227 in 2021/22, is low. Investigation showed this was a result of applying the restrictions to activity where the infusion of a monoclonal antibody had been explicitly specified in the SUS data (which is the coding approach we would recommend if routine adoption of either DMT is recommended by NICE). By removing the OPCS code restrictions of inclusion of either x891 or x892, the volume of activity increased to 530,402 in 2021/22. This is shown in table 2. Note removing this restriction, the price estimate increases to £535 at 2021/22 prices.

Table 2: Output of Price Estimate query by financial year using codes x292 only

Financial Year	Count	Total_Tariff_Initial_Amount	Average price
2018/19	268,750	142,726,726	531
2019/20	283,815	153,809,693	542
2020/21	422,207	223,568,212	530
2021/22	530,402	284,006,671	535
2022/23	586,570	320,180,539	546
2023/24	546,050	308,965,646	566

Applying the uplift factors for Covid, inflation, efficiencies and MFF gives a value of £589. Using more recent data for 2023/24 gives an unadjusted value of £566 and an adjusted figure of £688.

Table 3 shows the HRGs for which x292 code reports the most activity. For example, codes of FD02 and HD23 cover disease areas like Crohn's disease, colitis or rheumatology – areas known for the use of monoclonal antibody infusions.

Table 3 – HRG areas of activity by volume

HRG_Code	HRG_Name	Spell_Count
FD02H	Inflammatory Bowel Disease without Interventions, with CC Score 0	92,603
FD02G	Inflammatory Bowel Disease without Interventions, with CC Score 1-2	26,120
HD23J	Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 0-2	25,551
SA04L	Iron Deficiency Anaemia with CC Score 0-1	21,253
SA04K	Iron Deficiency Anaemia with CC Score 2-5	20,020
AA30F	Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1	18,849
AB18Z	Continuous Infusion of Therapeutic Substance for Pain Management	14,247
AB18Z	Continuous Infusion of Therapeutic Substance for Pain Management	12,748

HD23H	Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 3-4	12,645
HD24G	Non-Inflammatory, Bone or Joint Disorders, with CC Score 2-4	11,164
WJ11Z	Other Disorders of Immunity	10,457
SA30D	Plasma Cell Disorders with CC Score 2-4	10,095
HD24H	Non-Inflammatory, Bone or Joint Disorders, with CC Score 0-1	9,749
SA04J	Iron Deficiency Anaemia with CC Score 6-9	9,189
HD23G	Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 5-6	7,343
PF27A	Paediatric Inflammatory Bowel Disease with CC Score 1+	6,610
SA30E	Plasma Cell Disorders with CC Score 0-1	6,292
AA30E	Medical Care of Patients with Multiple Sclerosis, with CC Score 2-4	6,213
JA12L	Malignant Breast Disorders without Interventions, with CC Score 0-1	6,207
PF27B	Paediatric Inflammatory Bowel Disease with CC Score 0	6,069
WH19Z	Potential Health Hazard Related to Communicable Diseases	5,254
HD24F	Non-Inflammatory, Bone or Joint Disorders, with CC Score 5-7	5,230
SA09K	Other Red Blood Cell Disorders with CC Score 2-5	5,068
AA30F	Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1	4,807
SA30C	Plasma Cell Disorders with CC Score 5-7	4,745

Single Technology Appraisal

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	Gloucestershire ICB
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

We cannot comment, although we note that there appear to be gaps in the current evidence for clinical and cost effectiveness.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Yes. We agree that the summaries are an accurate interpretation of the evidence thus far.
We note that there appear to be gaps in the current evidence for clinical and cost effectiveness.
There remain concerns about the safety and efficacy of Lecanemab given the current evidence.
In addition, there is a lack of capacity and infrastructure in all local systems to ensure safe and equitable use of Lecanemab . Significant investment in local NHS services would be required to support safe and effective use.
We agree that insufficient benefits were demonstrated in clinical trials to justify a positive recommendation at this time.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Yes
We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs to the NHS, and that a negative recommendation is appropriate at this time.
We strongly agree with the decision not to recommend for managed access.
We do not agree that the cost of evidence generation activities should be borne by the NHS. This would result in funding for established services being diverted to fund an unproven treatment.

If NICE approve for use in the future, it is vital that a suitable funding variation is put in place to ensure system readiness. NICE need to work with NHSE to ensure that an implementation plan and associated funding are agreed and in place before publishing a positive TA. This is needed to ensure patient expectations are managed, and that a consistent approach is taken to implementing NICE guidance to avoid and variation in access to treatment and increasing health inequalities.
We have significant concerns about the high degree of uncertainties in both the clinical evidence and economic modelling and analysis. A negative recommendation needs to stay in place until these issues have been resolved.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

This would need to be considered as part of the funding variation.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

worth noting that the "control" data used by Eisai represent an external cohort so of questionable value

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Yes

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Yes

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability,**

religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

- **Comment**

I support the decision not to recommend. First, the data show only a very small treatment effect that is below the level considered to be evidence of minimal clinical benefit. Second, when the open label extension trial results are added, the rate of decline in treated and untreated groups is exactly the same. Taken together these data do not suggest either meaningful benefit or any long term disease modification. Allied to cost and side effect profile - downplayed by its proponents - it is hard to make a case.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	

Comments on the DG:

- **Has all of the relevant evidence been taken into account?**

You have not taken the effect of Alzheimer's dementia on the patient's family or on society as a whole. There is a severe cost of looking after patients with dementia in the severe phase. The longer someone stays in the mild phase, the cheaper it is to society.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

No as again the societal costs of dementia are excluded from your modelling

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Unlikely as it stops the NHS from researching the long term effects of the drug and moreover increases the cost of care which is borne by the social services and the NHS. The longer someone stays in the mid range, the less likely she is to then need older adult psychiatric care

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination**

against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

Draft guidance 2 consultation – Additional evidence

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Date completed	11 April 2025

1. Additional Economic Evidence and Updated Cost-Effectiveness Results

1.1 Summary and critique of company's changes compared with the ACM 2 company base-case

1.1.1 The company's updated base-case

The EAG was able to reproduce the company's new with the model provided, but was unable to exactly reproduce the old base-case when trying to revert the below list of company changes. The resulting difference in the ICER was approximately [redacted] (new model file vs old company ICER). This may be a result of the company not providing detailed by cell documentation of all their changes.

Changes to the model base-case include:

- Updated baseline distributions of patients across MCI and mild AD health states (adopted in new EAG base-case)
- Updated number of caregivers per patient (1.8) (adopted in new EAG base-case)
- Change of source for health state costs to Wittenberg et al. 2019 (not adopted in new EAG base-case)
- Applying treatment waning to all off-treatment health states, regardless of reason for discontinuation, using mean amyloid positron emission tomography (PET) levels from Clarity AD and amyloid re-accumulation rates (partly adopted in new EAG base-case)
- Use of patient-reported EQ-5D for MCI and mild dementia health states (adopted in new EAG base-case)
- Use of general population mortality for MCI (HR=1) (adopted in new EAG base-case)
- Use of Scottish Health Service APOE4 testing costs (adopted in new EAG base-case)
- Revised PAS

Unresolved issues:

- As stated in the previous EAG critique, the company's model predictions resulted in health state occupancy not in line with Clarity-AD or other health economic models in AD. As pointed out, the likely direction of bias would be in favour of lecanemab (as the model over-estimates the severe health state occupancy observed in Clarity-AD and as estimated by other economic models, and more so for SoC than for lecanemab). The EAG had requested that the company provide per year health state occupancy comparisons of their model estimates with those estimated by other models and alternative analyses, but this was not provided. The EAG wishes to draw attention to this issue which may induce bias to the extent of over-estimating cost-effectiveness of lecanemab versus SoC.

1.1.2 Alignment with donanemab appraisal (Comment 2)

1.1.2.1 Baseline distribution of patients across MCI and mild AD health states

The company have updated their baseline distributions to be in line with the donanemab appraisal, resulting in 20.4% of patients in MCI due to AD vs 79.6% of patients in mild AD, based on the starting distribution of the TRAILBLAZER trials.[1] This reduces the proportion of patients starting in MCI due to AD further – the EAG had used estimates of 38% versus 62%, which was based on the EAG's clinical

expert opinion. For comparison, real world data from the 2023 national audit of memory services indicated that out of all patients seen in memory service, 17% were diagnosed with MCI, compared with 71% who had any type of dementia.[2] Assuming that the remainder (those that neither had MCI nor any type of dementia) are not AD patients, this would translate to 24% vs 76%. It remains unclear whether these proportions are representative of those in patients with AD. In the absence of evidence for the starting distribution, assumptions have to be made. There is a view that more awareness of disease-modifying treatments (on the NHS) will lead to individuals coming forward earlier. The EAG thus uses the company's distribution in its base-case and explores the EAG's original distribution in a scenario.

1.1.2.2 Number of caregivers per patient

The company now assumes an average of 1.8 caregivers per patient with AD, which was based on the GERAS study[3] and in line with NICE ID6222 committee preferences. The EAG agrees that more than one caregiver may be involved per patient, but it also thought that whether the utility decrements applied to all caregivers in the same way was questionable, especially since the reported utility values from the GERAS study were obtained from the primary carer. The EAG accepts the increase in the number of caregivers based on this evidence, but notes the caveat that the impact on caregiver's HRQoL may be over-estimated if primary caregiver utility decrements are applied. The EAG therefore also explores assuming only 1 caregiver per patient in a scenario.

1.1.2.3 Health state costs

The EAG considers the company's change to using the Wittenberg et al study for health state costs acceptable.[4] However, there were discrepancies in the values reported by Wittenberg et al and those used in the company's model and the company's calculations were not provided. It was unclear whether the company excluded unpaid care costs, which are outside NICE's perspective and in alignment with the donanemab appraisal DG2. That is why the EAG continued to use the original health state costs sourced from Alzheimer's society research, excluding 47.2% of private care costs.

1.1.3 Infusion costs (Comment 3)

The NICE appraisal committee concluded that there is remaining uncertainty about the estimated cost of lecanemab infusion, but that the most appropriate cost was likely closer to the NHS England estimate based on the infusion cost for coronavirus monoclonal antibodies than the company's estimate.

The company in response to the DG2 attempted to understand the NHS England cost estimate and noted that this estimate included costs that are specifically for establishing COVID Medicines Delivery Units – which are not applicable for the administration of lecanemab. The EAG agrees that these costs should not be attributed to administration of lecanemab. An itemised breakdown is not available to the EAG or the company. The EAG considers that this may indicate that the NHS England cost may be higher than that expected for lecanemab administration, but also notes that there is still uncertainty about the resource use required for administration of lecanemab that would be additional to the ones required for administration of chemotherapy, given that lecanemab patients may have special needs, may experience adverse events, and that functional tests may need to be performed.

The company considers that it is unlikely to be the case that patients have more complex needs than those receiving cancer treatments, but the EAG considers that uncertainty remains about that, especially since some patients will have progressed to moderate or severe AD (in the company's model transitions from mild AD to severe AD are possible), which has not yet been identified (the company suggested

that infusion visits could be used for functional tests). The company state that adverse events are already included in the company's model separately and their costs should not be double-counted. The EAG notes that only pharmaceutical costs were included for the infusion-related reactions, and no additional staff time, and that inclusion of additional staff time may need to be considered. In addition, the EAG notes that the company stated that functional tests (for assessing the patients' health state and determine potential treatment discontinuation) could be carried out during routine lecanemab infusion visits and did not include costs for additional outpatient visits in its base-case.

To the EAG, there remains uncertainty about the appropriate infusion cost. Given the company's observations, the NHS England estimate may be high, but management of infusion-related reactions, some patients' complex needs and health state assessments using functional tests are not incorporated in the chemotherapy infusion cost nor the company's micro-costing. The EAG thus uses the NHS England estimate and only includes 6-monthly (as opposed to quarterly) outpatient visit costs in its base-case. Further information on the frequency of functional assessments at routine infusion visits and a detailed breakdown of NHS England cost estimates may be helpful. Acknowledging the uncertainty and the large impact, the EAG also explores using the company's micro-costing + overhead costs and chemotherapy code in scenarios.

1.1.4 Treatment effect waning (Comment 4)

As per DG2, the appraisal committee concluded that the most appropriate approach would include some treatment waning. It thought that it was inappropriate to assume treatment benefits would be lost immediately and completely after stopping treatment and it considered that scenarios exploring this assumption by the company and EAG were based on arbitrary figures, not on robust clinical expectations. In the absence of evidence on a continued treatment effect after treatment discontinuation, the company explored treatment effect waning by applying it to all patients that discontinue, regardless of their reason for discontinuation, with duration of waning based on time taken for amyloid to re-accumulate from different thresholds. The intention of the company was to align waning assumptions with observed clinical outcomes.

The EAG welcomed a new attempt at basing treatment effect waning assumptions in the model on existing evidence. However, after careful consideration, the EAG has come to the conclusion that the company's attempt only adds little information. The main concerns are:

- The company's attempt rests on the assumption that treatment effect is explained by levels of amyloid clearance only. The NICE DG2 stated that *"the clinical experts noted that the relationship between level of amyloid plaques and symptoms of Alzheimer's disease is unclear."* Similarly, the appraisal committee in the donanemab appraisal stated *"that change in amyloid is a disease biomarker but not a measure of clinical effectiveness"*.[5] The EAG notes that there are patients that respond well to lecanemab and others that do not respond well and queries whether these non-responders do not experience the same amyloid clearance as responders, or whether non response can occur irrespective of amyloid clearance. [redacted].[6] No evidence has been presented to show that response is contingent on amyloid clearance only. It is thus unclear how predictive the company's approach is of lecanemab treatment effect waning in clinical practice.
- The amyloid re-accumulation rate following lecanemab discontinuation was estimated at 2.6CL per year, which according to the company was observed in an off-treatment period in Study 201 and documented in the lecanemab SmPC. The EAG considers that rate very uncertain as

no information was provided on the sample size (that was likely small, given that only 87 patients completed the study period and not all of these continued in the extension phase) and the duration for which off-treatment amyloid re-accumulation was observed ([redacted]).[6] This rate may therefore be under-estimated, which means that the duration of treatment waning may be over-estimated.

- The EAG is concerned that the company's approach lacks face value. Median time to treatment discontinuation was [redacted] in the company's model (time to 10% on treatment [redacted]). The company's assumption implies that the full treatment effect is lost at [redacted] after treatment discontinuation, that is approximately at [redacted] after starting treatment. This appears implausibly high to the EAG without any evidence to support long treatment effect duration. In addition, due to the company's implementation, about [redacted] of patients off-treatment still experience the full treatment effect at approximately 16 years after starting treatment, while [redacted] of patients were already off-treatment at 7.5 years. The company's implementation thus appears to be biased. The EAG is also aware of the assumption by the donanemab appraisal EAG of continued full treatment effect for one year after treatment discontinuation, which was based on limited donanemab trial evidence. The donanemab appraisal EAG assumed a duration of treatment effect waning of 5 years, which was considered optimistic by the appraisal committee.

Given the uncertainties around the company's assumptions, the EAG concludes that the company's implementation of treatment effect waning adds little information. The EAG still has not seen any evidence for the duration of the lecanemab treatment effect. The EAG uses the company's implementation of treatment effect waning, but uses 1 year for the start of treatment effect waning (in line with the donanemab appraisal) and a 4 year treatment effect waning duration for the post-18 months group, and immediate treatment effect waning with a 4 year duration for the pre-18 months group. Given that during the treatment effect waning period the full treatment effect still applies (to a decreasing proportion of patients), the EAG considers that this may be optimistic.

1.1.5 Stopping rules (Comment 5)

The company's base-case included two stopping rules, 1) severity-based and 2) institutionalisation-based.

Regarding the severity-based stopping rule, the company continues to model patients in the moderate AD health state as having discontinued lecanemab treatment and the EAG considers this as appropriate but with the caveat that sufficient outpatient visits need to be included in the model to ensure that patients' progression to moderate AD is not missed. In a previous company scenario and EAG base-case, quarterly outpatient visits were thus included in the model. The company continues to only include these additional outpatient visits in a scenario and also reduced the frequency to every 6 months, because of expert opinion highlighting that functional tests could be carried out during routine lecanemab infusion visits (without any impact on costs). The EAG is unsure whether including functional tests during routine infusion visits is feasible and whether it would not result in additional costs: presumably functional tests require more or different staff time than infusion visit monitoring. The EAG concludes that monitoring is necessary for decisions on treatment continuation and this should be included in the base-case, but considers that whether 3- or 6-monthly outpatient visits are more appropriate is uncertain and may depend on whether the infusion visit costs include the appropriate staff and time required for performing functional tests. The DG2 on donanemab used 6-monthly outpatient visits, but highlighted uncertainty about this. Given that the EAG uses the higher NHSE preferred infusion costs in its base-case, it opted to include 6-monthly instead of 3-monthly outpatient visits.

It should be noted that the model features a one-month cycle length, which means that patients can transition to the moderate AD health state every month and then discontinue in the same month, while in practice patients may spend some time in the moderate AD health state before they discontinue. Treatment costs in the model are therefore likely under-estimated compared to clinical practice, which leads to likely over-estimation of cost-effectiveness.

Regarding the institutionalisation-based stopping rule, the company clarified that this was not a stopping rule as such but rather reflected what would happen in clinical practice, which was supported by some experts' opinion. The company also performed a scenario that allowed 10% of patients (which in the model have mild AD, since patients in the moderate AD health state are not modelled to take lecanemab) entering permanent care to remain on lecanemab treatment. The company stated that this was supported by recent clinical validation, the details of which were not provided. The EAG wondered whether the clinical experts that were consulted were presented with the fact that the question was about patients with mild AD that were admitted to permanent care, which is a small percentage (in the model on average [redacted] of all patients are both in the mild AD health state and in permanent care). The EAG acknowledges that there may be logistical challenges for administration of lecanemab when a patient is admitted to permanent care, which may mean that not all patients with mild AD in permanent care may have access to lecanemab. But the EAG did not see any evidence supporting the company's assumed 10%. The EAG thus assumed an arbitrary 50% in its base-case to acknowledge that not all patients with mild AD may be able to continue lecanemab treatment when in permanent care.

1.1.6 Disabling treatment effect for transition from mild to severe AD (Comment 6)

The EAG still considers it appropriate to disable the relative treatment effect that the company applied to the transition from the mild AD to the severe AD health state. This is because the company presented no evidence of a significant treatment effect in this transition, but also because, as noted above, the company's model already contains a bias that under-estimates the relative state occupancy in severe AD of lecanemab versus standard of care compared with the observed state occupancy in Clarity AD. For this reason, the EAG disables the relative treatment effect for the transition from mild to severe AD in its base-case.

1.1.7 Utility values (Comment 7)

The company used patient-reported utility values in the MCI due to AD and mild AD health states. Utility values were treatment independent. The EAG accepts the company's approach.

1.1.8 Caregiver utility (Comment 8)

The appraisal committee, company and EAG agree that the increment approach to including caregivers' HRQoL is appropriate. The remaining uncertainties lie in whether a) an additional utility decrement applies for caregivers when a patient is admitted to permanent care, b) the number of caregivers and c) the magnitude of the utility decrements for caregivers. Regarding a), the company presented no new evidence and the EAG maintains that an additional caregiver utility decrement upon institutionalisation is not supported by evidence and again disables this in its base-case. Regarding b) the company increased the number of caregivers to 1.8 to be in line with the donanemab TA as discussed in Section 2.1.2. Regarding c), the company provided a new scenario analysis addressing the potential under-estimation of caregiver utilities when the EQ-5D-5L is used, as the company highlights the lack of sensitivity of EQ-5D-5L for caregivers' changes in HRQoL and cites supporting evidence from Reed et al (2017) and results from Clarity AD for both EQ-5D-5L and the Zarit Burden Interview tool. The company performed a scenario analysis using alternative utility values derived from a vignette study

and used by the company in NICE ID6222. The EAG agrees that it may be that the impact on HRQoL may be under-estimated when using the EQ-5D-5L and only one caregiver. The EAG also noted that the appraisal committee in NICE ID6222 preferred the utility values from the GERAS study over the vignette study. The EAG also refers to its conclusion about the number of caregivers in Section 2.1.2, that the impact on caregiver's HRQoL may be over-estimated if primary caregiver utility decrements are applied and 1.8 caregivers are modelled. The EAG therefore considers that the company's scenario, which is also not in line with the NICE reference case, may over-estimate the impact on caregiver HRQoL. The EAG considers that despite a potential lack of sensitivity of the EQ-5D-5L, the EAG base-case likely appropriately captures the caregiver burden as it also includes more than just the primary caregiver, but acknowledges uncertainty about the caregiver burden. The EAG includes a scenario assuming only 1 caregiver per patient.

1.1.9 APOE4 testing costs (Comment 9)

The company were unable to verify the APOE4 test costs used in their previous model versions that were sourced from the NHSE BIA submission. The company identified an alternative estimate sourced from the Scottish Health Service costs, of £41.10 as opposed to the NHSE [redacted], which they used in a scenario analysis. The EAG considers this relevant, includes this in its base-case but also explores a scenario that uses the NHSE estimate.

1.2 EAG analyses

1.2.1 EAG base-case

As per the critique points above, the EAG made the following changes to the company's post ACM2 base-case (Table 1):

1. Health state costs: use Alzheimer's UK research and remove 47.2% private care costs
2. Infusion costs based on NHS England estimate
3. 6-monthly outpatient visits for monitoring
4. Treatment effect waning for pre-18 months group immediately, for post-18 months group after one year, with duration of 4 years
5. 50% of patients with mild AD in permanent care remain on treatment
6. Disable treatment effect on the transition from mild to severe AD
7. Disable additional caregiver disutility when patient moves to permanent care

1.2.2 EAG scenarios

The EAG explores the following main uncertainties in scenarios (Table 2):

1. EAG's base-case distributions to explore increase in patients presenting with MCI due to AD
2. Infusion costs based on chemotherapy code SB12Z
3. Infusion costs based on company's micro-costing + overhead
4. APOE4 testing costs based on NHS England estimate
5. Include 1 caregiver per patient

1.2.3 Cost-effectiveness results

Table 1: EAG amendments to post ACM2 company base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case post DG2							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,706
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Health state costs: use Alzheimer's UK research and remove 47.2% private care costs							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,023
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Infusion costs based on NHS England estimate							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,797
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
6-monthly outpatient visits for monitoring							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,995
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Treatment effect waning for pre-18 months group immediately, for post-18 months group after one year, with duration of 4 years							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,902
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
50% of patients with mild AD in permanent care remain on treatment							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,301
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Disable treatment effect on the transition from mild to severe AD							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,855
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Disable additional caregiver disutility when patient moves to permanent care							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,056
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG base-case							

Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77,148
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. The EAG base-case could not be run probabilistically (due to overwriting of EAG changes with default values – and an amendment to default values did not give correct results).							

Table 2: EAG scenarios conditional on EAG post ACM2 base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case post DG2							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77,148
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S1. EAG baseline distribution MCI due to AD and mild AD							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	79,779
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S2. Infusion costs based on chemotherapy code SB12Z							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,765
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S3. Infusion costs based on company's micro-costing + overhead							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,687
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S4. APOE4 testing costs based on NHS England estimate							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77,581
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S5. Include 1 caregiver per patient							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82,654
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. The EAG scenarios could not be run probabilistically (due to overwriting of EAG changes with default values – and an amendment to default values did not give correct results).							

2. References

[1] Collins E. Insights from TRAILBLAZER-ALZ 2 (donanemab): limited duration dosing. *AAIC*, 2024.

[2] Royal College of Psychiatrists. *National audit of dementia: spotlight audit in memory assessment services 2023/2024 [Internet]*. London: Royal College of Psychiatrists, 2024 [accessed 3.4.25]. 29p. Available from: https://www.rcpsych.ac.uk/improving-care/ccqi/national-clinical-audits/national-audit-of-dementia/national-audit-dementia-rounds-5-and-6/national-audit-dementia-round-6/memory-services-spotlight-audit-2023---national-report-publication

[3] Wimo A, Reed CC, Dodel R, Belger M, Jones RW, Happich M, et al. The GERAS Study: a prospective observational study of costs and resource use in community dwellers with Alzheimer's disease in three European countries - study design and baseline findings. J Alzheimers Dis 2013; 36(2):385-399

[4] Wittenberg R, Knapp M, Hu B, Comas-Herrera A, King D, Rehill A, et al. The costs of dementia in England. Int J Geriatr Psychiatry 2019; 34(7):1095-1103

[5] National Institute for Health and Care Excellence. *Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]: Draft guidance [Internet]*. London: NICE, 2025 [accessed 4.4.25] Available from: https://www.nice.org.uk/guidance/gid-ta11221/documents/html-content-9

[6] Eisai Ltd. *Clinical study report: a placebo-controlled, double–blind, parallel-group, bayesian adaptive randomization design and dose regimen–finding study, with an open-label extension phase, to evaluate safety, tolerability and efficacy of BAN2401 in subjects with early Alzheimer's disease (Study 201: Pt 1-5) [PDFs provided by the company]*, 2023 [accessed 13.12.23]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

Draft guidance 2 consultation – Additional evidence

Addendum to EAG critique

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1. Addendum with additional EAG analyses

1.1 Treatment continuation when entering residential care in mild AD state

NICE requested to explore that 100% of patients with mild AD remain on treatment when entering residential care. This scenario was performed conditional on the company and the EAG base-case.

1.2 Use of GERAS utility values for caregivers

NICE requested to explore a scenario in which caregiver utility values from the GERAS study were used, referring to ID6222[1], the NICE TA for donanemab, in which the GERAS study was the preferred source of caregiver utility values by the EAG and committee, and which was also the source for the company's estimate of 1.8 caregivers in this appraisal. The EAG agrees that the GERAS study is a relevant source to inform caregiver utility in this appraisal. The company had not submitted utility values from the GERAS study adapted to this appraisal (an adjustment was made by the EAG in ID6222). Due to time constraints, the EAG thus used the donanemab EAG's calculated utility values from their base-case, as reported in Table 5 on p29 of their critique of the company's response to NICE DG2 (ID6222). These utility values varied by health state (Table 1). This scenario was performed conditional on the company and the EAG base-case.

Table 1: Caregiver utility values

	Currently used in company's model for both arms	**Donanemab EAG adjusted utility values based on the GERAS study for both arms**
MCI due to AD	[redacted]	0.81
Mild AD	[redacted]	0.80
Moderate AD	[redacted]	0.79
Severe AD	[redacted]	0.76

1.3 Correction to EAG analysis

While implementing these changes, the EAG noticed that change 5 (that is on the proportion of patients with mild AD in residential care receiving treatment) was not carried forward in the combined EAG base-case results. This had a minor effect on the EAG base-case ICERs and scenarios based on this. The EAG thus corrected these analyses in below tables. Note that previously, scenario 1 (using this EAG's original base-case distributions to explore an increase in patients presenting with MCI due to AD) decreased the ICER, while now it increases the ICER, which is caused by the change in proportions of patients in the mild AD permanent care health state together with those patients now incurring treatment costs.

2. EAG analysis results

Table 2: EAG amendments to post ACM2 company base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case post DG2							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,706
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Health state costs: use Alzheimer's UK research and remove 47.2% private care costs							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,023
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Infusion costs based on NHS England estimate							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,797
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
6-monthly outpatient visits for monitoring							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,995
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Treatment effect waning for pre-18 months group immediately, for post-18 months group after one year, with duration of 4 years							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,902
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
50% of patients with mild AD in permanent care remain on treatment							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,301
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Disable treatment effect on the transition from mild to severe AD							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,855
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Disable additional caregiver disutility when patient moves to permanent care							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,056
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

EAG base-case*							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82,719
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. The EAG base-case could not be run probabilistically (due to overwriting of EAG changes with default values). *Corrected							

Table 3: EAG scenarios conditional on EAG post ACM2 base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82,719
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S1. EAG baseline distribution MCI due to AD and mild AD							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,707
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S2. Infusion costs based on chemotherapy code SB12Z							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,715
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S3. Infusion costs based on company's micro-costing + overhead							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,215
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S4. APOE4 testing costs based on NHS England estimate							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,151
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S5. Include 1 caregiver per patient							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	88,622
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S6. EAG base-case + 100% remain on tx in residential care if have mild AD							

Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	88,289
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S7. EAG base-case + Use GERAS utility for caregivers + 1.8 caregivers							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,659
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S8. Company base-case + 100% remain on tx in residential care if have mild AD							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,897
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
S9. Company base-case + Use GERAS utility for caregivers + 1.8 caregivers							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,962
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

All scenarios are corrected. S6-S9 are new scenarios requested by NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated.

3. References

[1] National Institute for Health and Care Excellence. Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]: Draft guidance [Internet]. London: NICE, 2025 [accessed 4.4.25] Available from: https://www.nice.org.uk/guidance/gid-ta11221/documents/html-content-9