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]

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2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Alzheimer's Research UK
   b. Alzheimer's Society
   c. Association of British Neurologists
   d. College of Mental Health Pharmacy
   e. Faculty of Public Health
   f. Royal College of Psychiatrists
   g. NHS England response on infusion pricing

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 **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

5. **Eisai Managed Access proposal**

6. **NICE Managed Access Feasibility Assessment**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments **5pm** on **Friday 20 September 2024**. 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	**Eisai's commitment to enabling access for NHS patients**

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	Since 22 August 2024 when the Medicines and Healthcare products Regulatory Agency (MHRA) granted a marketing authorisation in Great Britain, lecanemab is the first treatment for early Alzheimer's disease (AD) that targets an underlying cause of the disease to be authorised in a country in Europe.[1] This represents a step-change in the treatment of early AD, particularly for patients with MCI due to AD, for whom there are currently no pharmacological treatment options. Eisai (henceforth referred to as 'the company') welcomes the opportunity to comment on the draft guidance and provide additional information in support of eligible NHS patients in England and Wales having access to lecanemab as quickly as possible. The company welcomes confirmation that the Committee's preferred assumptions, where stated, align with the company base case, namely: • The overall model structure • The use of backwards transitions to represent transient movements to improved health states • The proportions of patients expected to be diagnosed through lumbar puncture and PET-CT scan • The proportion of patients tested for amyloid beta that will not have amyloid pathology The company has conducted further analyses to reduce uncertainty and enable the committee to make an informed judgement on the cost-effectiveness of lecanemab, aligning with EAG and/or committee preferred assumptions where these reduce or resolve uncertainty in the cost-effectiveness estimates or better represent current UK practice. Based on the aforementioned analyses, the company has made the following updates to the base case: • Alignment with the indicated population per the marketing authorisation granted by MHRA on 22 August 2024 (excluding apolipoprotein E ε4 [APOE4] homozygotes, described in further detail in comment 2, results reported in Appendix A.1.1) • Removal of serious AEs, due to overlap in the classification of severity and seriousness in Clarity AD and associated double-counting. Consequently, all serious AEs were already captured in the economic model through the AE data included by severity grades (comment 2) • Updated the baseline distribution of patients with MCI due to AD or mild AD to align with the EAG preferred assumption (comment 4) • Using the multistate survival model to estimate transition probabilities and incorporate time-dependent transitions, which the EAG suggested were more appropriate than constant transitions, and the committee suggested may provide results with better face validity (comment 6 and Appendix A.2.3)

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	• Use of the mortality hazard ratio for MCI due to AD reported by Crowell et al. (as per the original company submission), to produce mortality outcomes closer to the trial, as requested by the committee (comment 6 and Appendix A.2.10) • Modelling caregiver utilities as increments, rather than decrements, to circumvent the 'carer QALY trap', as this method does not penalise extended survival time (comment 9) • Inclusion of APOE4 testing costs for all patients tested, including those who do not go on to be treated with lecanemab (i.e., APOE4 homozygotes, comment 2 and Appendix A.2.7) • Updated the lecanemab administration cost based on a micro-costing conducted by the company, per the committee's request to explore alternative administration costs, considering a breakdown of required resource use (comment 10 and Appendix A.2.8) Finally, the company has proposed a revised Patient Access Scheme (PAS) (Appendix A.2.2.1) which demonstrates [redacted]. The updated base case ICER, as well as the individual and cumulative impact of each change, are shown in Table 22 in Appendix A.2.2.1. This revised PAS, in the form of a simple discount, [redacted] The company has also conducted additional scenario analyses (Table 26 in Appendix A.2.2.2.3), including: • Exclusion of APOE4 and amyloid beta diagnostic testing costs, to reflect that an estimated 90% of people would want to have an accurate diagnosis regardless of the availability of treatment, as noted in the draft guidance, thereby indicating the cost of diagnosis should not be borne by the company.[2] • Assuming a proportion (10%) of patients remain on treatment during institutional care (comment 7) • Inclusion of quarterly outpatient appointments for lecanemab treated patients to reflect the expected resource requirements of implementing the moderate AD stopping rule in practice. (comment 7) • Treatment effect waning for patients who discontinue due to all-cause discontinuation (comment 8) • An alternative discontinuation rate after 18 months (comment 8) • A reduction in non-medical health state costs, to reflect the proportion that may be borne privately (comment 11) • Use of constant transition probabilities (comment 6)

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	• Using Clarity AD open-label extension (OLE) data to inform the multistate survival model for months 18-36 (comment 6 and Appendix A.2.3.2) The results of the scenario analyses further demonstrate the plausibility for lecanemab to be cost-effective, with ICERs [redacted]
2	**Indicated population** Marketing authorisation for lecanemab was granted by the MHRA on 22nd August 2024 for MCI and mild dementia due to AD in adult patients that are APOE4 non-carriers or heterozygotes. Results for primary, secondary, safety, and key exploratory endpoints from the Clarity AD core study in the approved indication are presented in Appendix A.1.1. In addition, results from the Clarity AD OLE are presented for primary and safety endpoints in Appendix A.1.2. In the indicated population, lecanemab demonstrated a statistically significant effect on established, validated, and globally accepted endpoints, covering a range of cognitive and functional aspects. These endpoints represent clinically meaningful scales that directly measure how a patient thinks, feels, or functions, with every domain within the instruments being considered to measure a clinically meaningful concept for AD patients.[3] The strong efficacy findings for lecanemab in APOE4 non-carriers and heterozygotes in Clarity AD coupled with the well characterised safety profile and statistically significant differences in patient and carer health-related quality-of-life (QoL) unequivocally demonstrate the benefits of treating early AD patients with lecanemab (i.e. people with MCI due to AD or mild AD). The following inputs in the cost-effectiveness model have been updated to reflect the indicated population: • Clinical inputs: o Baseline characteristics (including age, percentage female, baseline CDR-SB distribution, and weight [mean weight and distribution of patients across weight bands])

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	o Time to worsening hazard ratios for MCI due to AD and mild AD, defined by CDR-SB and global CDR o Patient counts at 0-18 months to inform the state transition modelling scenario o Multistate survival analysis (MSM) o Discontinuation rate for MCI due to AD and mild AD o Adverse event rates ▪ As part of this update, serious AEs were removed from the model due to overlap in the classification of severity and seriousness in Clarity AD and associated double counting. All serious AEs were already captured through the severity grades included. This was identified by the company after the first committee meeting, hence this is the first opportunity available to the company to correct the model. • Quality of life inputs: o Patient and caregiver health state utilities, estimated through a mixed model for repeated measures (MMRM) • Cost inputs: o Compliance o APOE4 testing for all patients tested (including APOE4 homozygous patients). ▪ The cost components and unit costs are aligned with the NHS England BIA submission in the current absence of an HRG code or alternative cost, inclusive of one outpatient appointment and the cost of testing, and a separate genetic counselling appointment for APOE4 homozygous patients. Details of the unit costs, multiplier for testing of APOE4 homozygotes, sources, and assumptions are presented in Appendix A.2.7. The total estimated cost of APOE4 testing in the model is £[redacted]. All updated inputs are presented in Table 20, Appendix A.2.1.
3	**Clinically meaningful treatment effect (draft guidance 3.6)** The company would like to clarify that the statement made in Section 3.6 of the draft guidance that *"the observed treatment effect for lecanemab at 18 months was about half of the treatment effect that is seen with current treatments at 6 months",* based on a statement by the EAG's clinical expert (pages 19-20 of the EAG report), is misleading. The draft guidance rightly caveats this, reiterating explanations by patient and clinical experts during the appraisal committee meeting as to why it is inappropriate to directly compare the treatment effect of lecanemab, a disease-modifying treatment, with that of acetylcholinesterase inhibitors and memantine, which are only symptomatic and have a different mechanism of action.

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	In addition, the statement given by the EAG's clinical expert was based on a comparison of the change from baseline for symptomatic treatments alone versus the difference in change from baseline for lecanemab versus symptomatic treatments. Therefore, the stated magnitude of difference in observed treatment effect for lecanemab versus symptomatic treatments in the draft guidance is incorrect. The company would like to highlight statements from the Alzheimer's Research UK (ARUK) submission, outlining the benefit for patients and their carers of extending time in milder AD states, highlighting the clinical meaningfulness of lecanemab treatment effect. ARUK stated that if people could access new disease-modifying treatments, then the typical pattern of decline experienced by those living with AD could be changed, improving a person's ability to function independently for longer and stopping worsening of symptoms. Further, they stated that maintaining individual independence over an extended period could also have positive implications for those supporting loved ones, such as allowing carers to sustain employment and improving the well-being of families affected by dementia, resulting in overall benefits to the economy. Per the committee's request to resolve uncertainty in the heterogeneity of results, the company has provided results for the following in Appendix A.1: • The distribution of change in CDR-SB score from baseline at 18 months, compared for lecanemab and placebo arms (Appendix A.1.3.1, Figure 13). • The mean difference from baseline by treatment arm at 18 months for the six individual domains of CDR-SB (Appendix A.1.1.1.1, Table 1). • The adjusted mean change from baseline in EQ-5D-3L health-related quality-of-life values, by treatment arm, analysed using a mixed effects model with repeated measures (Appendix A.1.1.2.1.4, Table 9). o Note, the committee request in the draft guidance was for the least-squares mean change from baseline in EQ-5D-5L analysed by MMRM. The company had already provided EQ-5D utilities analysed using MMRM. Having queried whether the committee wanted to see adjustment for additional covariates in the MMRM, or whether they would like to see the adjusted mean change, it was confirmed that the adjusted mean change from baseline in EQ-5D-3L utilities was appropriate, hence this has been provided. The distribution of change from baseline in CDR-SB score at 18 months, compared for lecanemab and placebo arms, is presented through the proportion of patients with cognitive and/or functional worsening at 18 months for lecanemab and placebo, categorised by no decline, any decline (decline of ≥0.5), and decline in CDR-SB in 0.5-point increments from ≥1 to ≥3 (Appendix A.1.3.1, Figure 13). Fewer lecanemab patients declined compared to placebo, regardless of the threshold applied from 0.5 to a 3-point cognitive and/or functional worsening. For example, for patients that progressed by 1.5-points or more (≥1.5) at 18 months, [redacted] of placebo patients declined compared to [redacted] of lecanemab patients, resulting in a relative risk reduction of [redacted]. These results translate into meaningful relative risk reduction of clinical decline with lecanemab treatment compared to placebo at 18 months.

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	Results are also provided for APOE4 and age subgroups (comment 5); lecanemab reduced the risk of progression versus placebo in all subgroups and across every threshold at 18 months, except for [redacted] subgroup where the proportions of patients worsening are similar ([redacted]). These results are discussed further in comment 5 (Appendix A.1.3.1). Lecanemab also showed statistically significant benefit in the adjusted mean difference versus placebo across all six CDR-SB domains, including memory, orientation, judgement/problem solving, community affairs, home and hobbies and personal care. The adjusted mean change from baseline was consistently lower for lecanemab compared with placebo across all six domains (Table 1 of the appendix,). These results show the treatment effect of lecanemab at 18 months compared to placebo is consistently significant across domains and that lecanemab provides manifold benefits to patients. Overall, these results demonstrate a consistent treatment effect of lecanemab across CDR-SB domains and levels of cognitive and/or functional worsening by 18 months in the indicated population and in APOE4 and age subgroups. Therefore, the company do not consider the results to be heterogeneous. Similarly, the adjusted mean change from baseline in EQ-5D-3L utility values, presented in Appendix A.1.1.2.1.4, Table 9, show that patients receiving lecanemab experience more improvement in their quality of life compared to placebo at 18 months in the patient self-reported survey, and less decline in their quality of life in the patient-by-proxy survey. The differences in the direction of changes between the patient self-reported survey and patient-by-proxy survey utility values are discussed in the health state utilities section (comment 9). The adjusted mean change from baseline at 18-months in EQ-5D-3L study partner's utility values indicated that carers of patients treated with lecanemab experienced marginally more decline in quality of life compared to carers of patients treated with placebo. However, at 12 months, this was reversed, as carers of patients treated with lecanemab experienced minimal decline relative to baseline. Moreover, the 18-month results are inconsistent with the notion that carer's quality of life is better when patients are in milder disease states. This is in line with findings presented by Reed *et al.* (2017), that the EQ-5D is a suboptimal measure of the quality-of-life impact of caring for people with AD, and the Zarit Burden Interview may be a more appropriate measure.[4] This is discussed in more detail below in the health state utilities section (comment 9).
4	**Trial generalisability (draft guidance 3.8)** Following the committee's request for estimates from clinical experts on what the introduction of lecanemab would do to the number of people who are diagnosed with MCI or mild dementia caused by AD, the company sought further expert feedback. The clinical experts (n=3) agreed that the proportions used in the original company base case, based on the baseline proportions in Clarity AD as defined by CDR-SB, would be reflective of UK clinical practice over time following the introduction of lecanemab.

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	All clinical experts expected the proportion with MCI due to AD would increase over time due to knowledge of and access to treatment(s) for early AD, leading to an increase in people presenting to Brain Health/Memory clinics, as well as access to blood-based biomarkers and improvements in the mechanisms of identifying patients. One clinical expert stated that the proportions of patients initiating treatment with lecanemab would initially reflect the EAG's estimates (i.e., more patients with mild AD than MCI due to AD), as patients with mild AD would already be "on the books of clinics" (i.e., are more likely to already have a diagnosis). Moreover, as acknowledged in the draft guidance, MCI due to AD is rarely diagnosed (Section 3.2). Considering this feedback, the company has adopted the EAG's estimates of the baseline distribution of patients across health states (MCI due to AD = 38.3%, mild AD = 61.7%) in the updated base case to reflect expected UK clinical practice at the point of lecanemab reimbursement and over the short to medium term. The impact of this change on the ICER is presented in Appendix A.2.2.1.1.
5	**Treatment effects for subgroups (draft guidance 3.9)** Per the committee's request for the distribution of the CDR-SB for different subgroups, these data are presented for APOE4 (non-carriers, heterozygotes) and age (<65 years, ≥65 to <75 years, ≥75 years) subgroups in the same format as for the indicated population (comment 3), through the proportion of patients with cognitive and/or functional worsening at 18 months for lecanemab and placebo, categorised by no decline, any decline (decline of ≥0.5), and decline in CDR-SB in 0.5-point increments from ≥1 to ≥3, in Appendix A.1.3.1. Results are generally consistent across subgroups and with the indicated population. Across these subgroups, fewer lecanemab patients declined compared to placebo, regardless of the threshold applied from ≥0.5 to a ≥3-point worsening in CDR-SB, other than in patients less than 65 years old for the ≥1 threshold where the proportions are similar ([redacted]). Therefore, there is a meaningful relative risk reduction of clinical decline with lecanemab treatment compared with placebo at 18 months across the different age and APOE4 subgroups.
6	**Transition probabilities (draft guidance 3.12-3.13)** ***Estimation of transition probabilities*** The company acknowledge comments by the EAG and committee regarding the appropriateness of assuming constant transition probabilities. The company sought to address these during the response to clarification questions through multistate survival modelling, which the EAG considered to be appropriate, and provided a scenario analysis in which transition probabilities change over time. The company believes there is also evidence of time-dependency based on the smoothed hazard plots for the indicated population (A.2.3.1, Figure 23), and has therefore adopted the multistate survival model in the base case to estimate transition probabilities which vary over time, to align with the EAG's preference. Full details of the multistate model are presented in Appendix A.2.3.

	In addition, the multistate survival model implicitly handles competing risks as patients may either make the transition of interest (i.e., experience an 'event'), be censored at the end of the study, or be censored when they experience a movement to a competing health state. As such, patients are not censored from the entire analysis, only from one of the possible transitions. After a competing event occurs, patients contribute to the risk of making a different transition.[5] For instance, a patient who transitions from mild AD to moderate AD would then contribute to the analysis for the moderate AD to mild AD transition. Thus, the multistate model appropriately handles competing risks. Furthermore, as this multistate model structure (as described in the response to clarification question 8d) permits a maximum of two transitions from each health state, this circumvents the need to revise the model structure to align with the first solution proposed by Gidwani *et al.* 2020, such that each node only has two transitions, as suggested by the EAG and requested by the committee. As such, the company has not provided this scenario. The company hope that use of the multistate survival model in the base case resolves the EAG's concerns surrounding face validity of the constant transition probabilities and the possibility of errors in transition probability estimation due to inadequate handling of competing risks. ***Model outcomes and mortality benefit consistent with the trial data and clinical expectations*** The company acknowledge the committee's request for outcomes and mortality benefit that are consistent with the trial and clinical expectations. The company maintain that the health state occupancy in the original CS (B.3.14.2) was broadly consistent with the trial, as differences between the model and trial outcomes were small in absolute terms (within 5% for both lecanemab and placebo). Moreover, such differences are to be expected given transitions to severe AD and mortality were estimated from published literature due to insufficient events in Clarity AD, with data from Potashman *et al.* used to inform transitions to severe AD, and from Crowell *et al.* (2023) and UK life tables to inform mortality. Since the original CS, the model has been updated as follows: • The population has been updated to exclude APOE4 homozygotes to align with the licensed population. • The company has accepted the EAG's preferred estimates for the proportion of MCI due to AD and mild AD patients entering the model. Consequently, these no longer align with the baseline proportions in Clarity AD. • The company has adopted the multistate survival model in the base case, as described above. Therefore, health state occupancy predicted by the latest economic model differs from that presented in the CS. Graphs illustrating health state occupancy for the latest economic model compared with Clarity AD are presented in Appendix A.2.9. To enable this comparison and validate the modelling approach, the health state occupancy graphs have been produced using

	the baseline proportions of MCI due to AD and mild AD patients from Clarity AD, as defined by CDR-SB (78.6% MCI due to AD, 21.4% mild AD). For both lecanemab and placebo, the outcomes from the model remain broadly aligned with Clarity AD, as illustrated in Figure 45 and Figure 46 (Appendix A.2.9), as differences in health state occupancy in the model compared with Clarity AD at 18 months are all within [redacted] for both lecanemab and placebo. As with the state transition model used in the original CS, small differences are to be expected given the base case modelling approach, for which external data sources are used to inform mortality. Health state occupancy is underestimated for MCI due to AD and mild AD in the model versus the trial for both lecanemab and placebo, and overestimated in moderate AD, severe AD, and death, however these differences between arms are small ([redacted] in death, [redacted] in moderate and severe AD, [redacted] in MCI due to AD, and [redacted] in mild AD) for Clarity AD vs. CEM, lecanemab vs. SoC (Tables 52-54, Appendix A.2.9). To address the committee's request for transition probabilities in the model that lead to mortality benefit consistent with the trial data, the company explored different mortality scenarios from the original CS to consider if any were better aligned with Clarity AD. Using the mortality hazard ratio for MCI due to AD reported by Crowell *et al.* (0.63), rather than assuming this is equal to the general population, produces mortality closer to Clarity AD; outcomes were [redacted] closer for lecanemab and [redacted] closer for SoC at 18 months (Appendix A.2.10, Table 56). Whilst this reverts from the assumption adopted in the CS addendum submitted in April 2024, the company considers this appropriate because it ensures consistency of mortality risk in each health state with the model reported by Crowell *et al.* Therefore, the Crowell *et al.* 2023 mortality hazard ratio has been used for MCI due to AD in the base case. Only [redacted] deaths occurred over 18 months in Clarity AD, translating to a monthly probability of [redacted] This is expected given the follow-up period, age of the cohort and prognosis of early AD patients. As such, mortality was modelled using external data to enable the well-established increasing mortality risk with disease severity to be incorporated.[6–9] Whilst a mortality benefit was not observed over the 18-month Clarity AD core study follow-up, the available external data consistently indicates an increased mortality risk with more severe disease status, thus the company believes the approach to modelling mortality aligns with clinical expectations. However, given the committee request for state occupancy and mortality benefit consistent with the trial, the company has conducted a scenario analysis in which the mortality data from Clarity AD are used directly for the first 18 months in the economic model. Given mortality risk was calculated based on patients' baseline health state, probability of death for moderate and severe AD could not be calculated directly from Clarity AD. Instead, relative differences in mortality HRs from Crowell et al. for moderate AD and severe AD were calculated as multipliers to apply to the probability of death from Clarity AD. The moderate AD versus mild AD multiplier was applied to the probability of death for mild AD from Clarity AD to calculate probability of death for moderate AD, to which the severe AD versus moderate AD multiplier was subsequently applied to derive probability of death for severe AD. These calculations and the associated probability of death for each health state are reported in Table 55 in Appendix A.2.10. The resulting MCI due to AD and mild AD health state occupancy and mortality (Figures 47 and 48 in Appendix A.2.9 and Table 56 in Appendix A.2.10) are more closely aligned with Clarity AD for both lecanemab and SoC, which is to be expected given the Clarity AD mortality data are used

	directly. This yields a reduction in the ICER of £[redacted], suggesting the source of mortality data, whilst improving the fit of the economic model to Clarity AD, does not materially impact cost-effectiveness. Given the small impact on cost-effectiveness and to ensure the economic model reflects UK mortality (via the use of UK life tables combined with Crowell et al. HRs), the company has not used the Clarity AD mortality data in the base case. As requested by the committee, disaggregated, discounted, and undiscounted results for the company's base case, by modelled health states, are presented in Appendix A.2.2.3.
7	**Stopping rules (draft guidance 3.14)** **<u>Moderate AD</u>** The SmPC states that "treatment with lecanemab should be discontinued once the patient progresses to moderate Alzheimer's disease".[10] To address the committee's request for further information regarding how a stopping rule at moderate AD would be applied in practice, and confirmation that any resource implications of implementing this stopping rule are captured in the model, the company consulted three clinical experts and NHS England.[11] One expert indicated that they would not expect differences in staging practices for lecanemab patients compared to those receiving existing standard of care treatments but stated that this "may change with the availability of blood biomarkers to monitor progression". Additionally, two experts suggested that staging could be conducted concurrently with lecanemab infusion visits using straightforward cognitive tests, such as the Montreal Cognitive Assessment (MoCA). These assessments could be administered by various NHS staff bands without being resource-intensive or adding significant burden for patients. [redacted]The company therefore believe a stopping rule at moderate Alzheimer's disease is feasible and practical. In accordance with the feedback from NHS England, the company has conducted a scenario analysis in which patients have quarterly outpatient appointments whilst receiving lecanemab to reflect the expected resource requirements of implementing the moderate AD stopping rule in practice. However, considering the feedback from two experts that staging could be conducted concurrently with lecanemab infusion visits, this scenario may overestimate the resource required to implement this stopping rule, hence the company has conducted this as a scenario analysis rather than in the base case. The company consulted the NHS England BIA submission for an appropriate outpatient appointment cost, which used HRG code WF01A, elderly medicine service and stated that the elderly medicine service was used to "give an estimation of cost". Therefore, the same HRG code was used (WF01A, Non-Admitted Face-to-Face Attendance, Follow-up, Consultant Led) from the

	National schedule of NHS costs 2022/2023. However, the company selected the code specific to the Neurology Service, given monitoring for progression to moderate AD would occur via this service, rather than the general elderly medicine service. The cost of WF01A, Neurology service, is £222.92. This yields an [redacted] in the ICER of £[redacted] compared to the base case (Appendix A.2.2.2.3). **Institutional care** Whilst the company acknowledge the committee's conclusion that it would not be appropriate to apply a stopping rule upon entry to institutional care, the company would like to reiterate the consensus among UK clinical experts at the July 2023 advisory board that patients should not be treated with a disease-modifying therapy such as lecanemab in institutional care (Company Submission, Document B, section B.3.3.3.2). One expert noted that continuing treatment in this setting "would not be appropriate", while another described it as "bad practice". However, acknowledging the committee's concern that such a stopping rule could lead to increasing health inequalities, the company consulted additional clinical experts to determine whether some patients in MCI due to AD and mild AD would be expected to continue treatment with lecanemab whilst in institutional care. All three experts commented that the reason for entering institutional care should be considered in the decision, 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. In addition, one expert confirmed they would not expect patients to continue treatment with lecanemab once they had been institutionalised, and another stated that discussion of discontinuation would be reasonable for patients who have entered residential care because of their disease. The company would like to highlight that 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.[12] Thus, patients who enter institutional care health states in the model reflect those requiring permanent, not temporary care. Those who temporarily enter institutional care for respite, and may continue lecanemab per clinical expert opinion, therefore do not enter institutional care health states and, hence are inherently captured in the community health state occupancy. In addition, two experts commented that they would expect few patients with early AD to enter institutional care, estimating 5-10%. This aligns with the modelling approach, as the probability of admission to institution during mild AD (over 6 months) is 3.0%, as reported by Knapp et al. As such, the company believe the base case approach in which patients entering institutional care based on Knapp et al. discontinue treatment is appropriate, and this is consistent with clinical expert opinion. Importantly, the company also believe this does not translate to a stopping rule in which all patients who enter institutional care must discontinue, which reduces potential health inequality concerns. Irrespective, the company has presented a scenario in which 10% of patients remain on treatment following institutionalisation, to explore any residual variability in clinical decision-making and patient care. This yields an increase in the ICER of £[redacted](Appendix A.2.2.2.3).

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8	**All-cause discontinuation, treatment waning (draft guidance 3.15)** The company acknowledge the committee's request for scenarios exploring treatment-effect waning for patients who discontinue treatment in the MCI due to AD and mild AD health states. The company would like to reiterate that the base case conservatively assumes [redacted]. A scenario analysis has been conducted in which [redacted] to reflect the mechanism of action and clinical expert opinion (discussed further in this section). The company do not believe it is appropriate to apply treatment waning assumptions for patients discontinuing lecanemab due to all-cause discontinuation. All-cause discontinuation reflects discontinuation for any reason, whether clinical or non-clinical. Non-clinical reasons include patient choice, lost to follow-up, or withdrawal of consent, whilst clinical reasons include adverse event or inadequate therapeutic effect. In Clarity AD, [redacted] of lecanemab patients in the indicated population discontinued treatment during the core study, but none discontinued due to inadequate therapeutic effect. Of those that discontinued lecanemab treatment, [redacted] were for the non-clinical reasons listed above. The remainder discontinued for safety ([redacted]) or other ([redacted]) reasons.[13] Thus, by definition, as none of the discontinuations were due to inadequate therapeutic effect, these patients have not lost response to treatment. The current base case, in which an explicit waning assumption is not applied to the lecanemab treatment effect for patients who discontinue due to all-cause discontinuation until they reach moderate AD, reflects clinical expert opinion that a maintained treatment effect is clinically plausible. As noted in the draft guidance, clinical experts stated in the appraisal committee meeting that "*it is highly implausible that a person's condition will immediately worsen after stopping treatment with lecanemab*", due to the mechanism of action. By targeting amyloid beta, lecanemab subsequently inhibits the amyloid cascade, the trigger for the pathological effects seen in Alzheimer's disease. The effects of lecanemab on the amyloid cascade are evidenced through data on amyloid positron emission tomography levels in Clarity AD (Appendix A.1.1.1.2.1), which reduced to [redacted] Centiloids in the lecanemab arm of the Clarity AD core study at 18 months, below the 30 Centiloids threshold for amyloid negativity in Clarity AD, which is considered a 'normal' level. Following the first appraisal committee meeting, the company asked the clinical experts to elaborate on their statement. Both experts indicated they would expect to see a continued effect while plaque levels remained low, 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 2.6 CL per year to [redacted] CL per year across studies, and align with the estimated natural time course of amyloid accumulation of approximately 3.3 CL per year observed in the amyloid-negative stage of AD.[10,14–18] To further investigate the appropriateness of applying treatment waning to all-cause discontinuations, the company reviewed a recently published analysis by Trigg *et al.* (2024), which examined the implementation of treatment effect waning in NICE technology appraisals published

between October 2021 and September 2023.[19] The authors concluded that there was considerable variability in implementation across technology appraisals, with the most common reason for inclusion of waning being precedent from prior appraisals, and other reasons being lack of clinical plausibility for a sustained treatment effect. The majority of waning scenarios explored were based on the time from randomisation, and none applied treatment waning following all-cause discontinuation. Only nine of the 123 TAs reviewed by Trigg *et al.* applied any waning within the first two years. The most common waning start point was five years. The authors concluded the inclusion of treatment effect waning should be approached with caution as it "*may lead to the incorrect or unfair rejection of a technology if treatment effect waning assumptions have been applied with a lack of evidence."*

The company therefore considered precedent from NICE appraisals in AD; in TA217 of donepezil, galantamine, rivastigmine, and memantine for the treatment of AD, the Assessment Group did not apply treatment waning assumptions and the benefit was assumed to be maintained.[20]

Additionally, Trigg *et al.* recommend that "*treatment effect (or some effect) is sustained beyond discontinuation for people who stop treatment, when it is clinically plausible for lasting benefit to remain*." This is consistent with the clinical expert opinion that treatment effect would be maintained following discontinuation, attributable to the mechanism of action of lecanemab, and with the lack of any patients discontinuing due to inadequate therapeutic effect in Clarity AD.

Based on precedent from NICE appraisals in AD to assume no treatment effect waning following discontinuation, the clinical plausibility for a maintained treatment effect following discontinuation as stated in the draft guidance, and the conclusions of Trigg et al., the company maintain that it would not be appropriate to apply treatment effect waning to all-cause discontinuations.

However, to address any residual uncertainty, the company explored the feasibility of the committee's request to consider treatment waning following all-cause discontinuation, and has conducted a scenario analysis in which [redacted]

[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 modelling this scenario. First, the proportion of patients eligible for waning at each cycle was calculated based on the time spent in the health state [redacted] Then, the corresponding treatment effect to apply was calculated. The result is an overall health state waning proportion that [redacted]

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	[redacted] With this simplified approach, patient movement into and out of the health state over time is not accounted for. This scenario has minimal impact on the ICER, [redacted] it by £[redacted] compared to the base case (Appendix A.2.2.2.3). In light of the numerous uncertainties and assumptions required, the limitations identified by Trigg et al., and the absence of precedent for such an assumption in AD, the company maintain that this is not a valid scenario and should not be adopted in the base case. In addition, a scenario analysis has been conducted in which residual benefit is assumed following discontinuation of lecanemab at progression to moderate AD. While this is not adopted in the base case due to the limited data available to inform this effect at this time, the company believe some residual benefit is plausible due to the mechanism of action and expert opinion described above, and has therefore [redacted] This is presented alone, and in combination with the waning scenario described above. The associated ICERs [redacted] and [redacted], respectively (Appendix A.2.2.2.3). The committee also noted uncertainty surrounding the all-cause discontinuation rate after 18 months. To address this, the company has presented a scenario in which the all-cause discontinuation rate after 18-months is based on 36-month data from the Clarity AD open label extension study, as per the committee's request. This yields an [redacted] in the ICER of £[redacted] (Appendix A.2.2.2.3).
9	**Health state utilities (draft guidance 3.16)** To fulfil the committee's request for a detailed outline of the utility values used for each health state, their sources, and the justification for that source, these details are presented in Table 42 of Appendix A.2.5. In addition, in response to the committee's request, the company has provided further information on the use of patient-by-proxy utilities, consideration of adaptation by people with AD, and the approach to modelling caregiver quality of life. ***Patient health state utilities*** As requested by the committee, further exploration of the appropriateness of patient-by-proxy utilities, including consideration of adaptation by people with AD and their carers, is presented below. A hand search was conducted to explore whether patients adapting to AD (i.e., adapting to the symptoms of their condition, thus not recording their quality of life relative to perfect health thereby resulting in inaccurate self-reported quality of life), may contribute to the differences observed in self-reported and proxy-reported QoL (see CS B.1.3.4.1 for description of differences). Terms used in the hand search included "disability paradox" or "adaptation" each in combination with "Alzheimer's disease". In addition, a review of NICE appraisals published between 2019 and 2024 was conducted to understand how previous TAs considered the "disability paradox" when using proxy utilities. The terms "caregiver", "proxy", and "disability paradox" were used to identify relevant appraisals of

	diseases in which patients require caregiving and understand precedent for committee assumptions. The findings of the hand searches indicate that the concept of adaptation is not well understood and overall, were inconclusive with regards to how adaptation may impact patient-by-proxy utilities. Conde-Sala et al. conducted a three-year longitudinal study into discrepancies between patient and caregiver ratings of QoL for patients with AD. Their findings suggested that adaptation may contribute to differences in QoL in early stages of disease, stating that the positive ratings of patients can be understood in terms of psychological mechanisms, the disability paradox, or processes of "self-maintaining" and "self-adjusting", whilst negative ratings of caregivers can be explained by the impact of the diagnosis and the functional and behavioural changes in the patient, leading to greater burden. Notably, the authors concluded that in later stages of AD, adaptation is not sufficient to explain differences in reported QoL. Patients' 'overly positive view of their quality of life' is instead attributed to anosognosia and increased neurological deterioration, leading to patients perceiving their QoL to be considerably different from their actual status.[21] This aligns with findings from a meta-analysis of EQ-5D utility estimates by Landeiro *et al*. discussed in the CS (B.3.4.4). This study found that patients with severe AD still self-reported relatively high utilities, whereas the patient-by-proxy utilities indicated QoL for these patients was much lower. One of the papers identified (De Hond *et al.*) suggested that adaptation may be observed in patients with functional limitations. However, the authors noted the mechanism of the effect was unknown, i.e., whether a true change in QoL had occurred, or whether differences could be attributed to scale recalibration, i.e., adaptation.[22] As the study considered older patients with functional limitations only, not those with cognitive impairments, it is unclear whether the findings are relevant to patients with AD. Only one NICE appraisal was identified that discussed adaptation; HST25 (lumasiran for treating primary hyperoxaluria type 1). Adaptation was considered in the context of differences in utilities from adult and paediatric subgroups, rather than suitability of self-reported vs. proxy-reported utilities. Of the recent NICE TAs identified which considered proxy utility values, none discussed adaptation within the committee papers.[23,24] There is precedent for the use of proxy utilities in AD: in TA217, proxy values were deemed appropriate for all health states by the Committee.[20] Irrespective, a scenario is presented in Appendix A.2.2.2.3 using self-reported utilities for the MCI due to AD and mild AD health states. The results demonstrate that the use of self-reported rather than proxy utilities for these health states has an immaterial impact on cost-effectiveness, [redacted] the ICER by £[redacted]. Therefore, any potential impact of adaptation does not translate into decision uncertainty. The findings from Conde Sala et al. suggest that the estimation of a higher utility for mild AD than MCI due to AD based on self-reported data from Clarity AD may be due to the confounding impact in AD from patient neurological deterioration and anosognosia.[21] Given this potential confounding, the lack of conclusive evidence for an adaptation effect in AD and the negligible impact of using self-reported utilities for MCI due to AD and mild AD on the ICER, the company maintain that patient-by-proxy utilities are appropriate for all patient health states. This is supported by Landeiro *et al,* feedback in the UK HTA advisory board (July 2023, CS B.3.4.4.1) and further clinical validation in July 2024 that patient-by-proxy utilities provide more useful insights than self-reported

	utilities given the potential loss in accuracy for the latter due to cognitive decline (see Table 42, Appendix A.2.5 for more detail).[11] ***Application of caregiver utilities*** In response to the committee's request for clarity on the approach used for modelling utility values and further justification, the company revisited the approach used for modelling caregiver utilities. As discussed in the CS (B.3.4.4.2), the most appropriate method to apply caregiver utilities in cost-effectiveness analyses is not well defined. Two options were explored in the CS; the decrement approach in the base case (see CS B.3.4.4.2), and the additive approach in a scenario analysis. Pennington *et al.* (2024) highlight controversies in the choice of attaching either carer utilities or disutilities to patient health states and the ethical judgement that is therefore required to determine whether the carer should be included after the patient dies. The decrement approach results in the issue known as the 'carer QALY trap', through which a patient dying implies caregiver quality of life improves as the utility decrement ceases to be incurred. The additive approach requires the assumption that society places no value on the bereaved carer, as it is implicitly assumed that the carer either dies or survives with zero utility when the patient dies, an approach that was criticised by the EAG in the appraisal of risdiplam for the treatment of spinal muscular atrophy (TA755).[25,26] Given these limitations of both methods, the company continued to seek a solution and identified a utility increment approach, building on methods explored in previous NICE appraisals (TA386 and TA534) identified in Pennington (2020).[27] The increment approach aligns with patient and caregiver preferences by valuing interventions that enhance quality of life and cognitive function, and importantly, those that are estimated to delay progression and extend life, such as lecanemab. For the increment approach, the 'worst' health state (severe AD, institutional setting) is used as a reference, and utility increments are calculated relative to this health state for all remaining health states. The result is that extended survival time is not penalised with a caregiver utility decrement, and this also circumvents the assumption required for the decrement approach that caregiver quality of life improves upon a patient's death, thus mitigating the carer QALY trap. Given these methodological benefits, the increment approach has been adopted in the base case analysis. Utilities derived using the increment method and the decrement method are presented in Appendix A.2.5.1, Table 43 for comparison. In addition, evidence from Reed *et al.* (2017) suggests EQ-5D-5L may be a suboptimal measure of the quality of life of carers of people with AD, due to its focus on physical health (discussed in Appendix A.1.1.2.1).[4] Results from Clarity AD support this; while carers of patients treated with lecanemab had experienced minimal decline in EQ-5D relative to baseline and less decline than placebo at 12 months, a greater decline was seen at 18 months for caregivers of patients treated with lecanemab compared to placebo ([redacted]% more decline, non-significant). This contrasts with the statistically significant difference for lecanemab vs. placebo at 18 months observed for caregiver Zarit Burden Interview (ZBI), which demonstrated [redacted]% less decline for caregivers of patients treated with lecanemab (Appendix A.1.1.2.3), aligning with the statistically significant clinical improvement observed in Clarity AD across all primary and secondary endpoints. ZBI is a tool focused specifically on assessing caregiver burden, using interviews to evaluate the stresses experienced by caregivers of people with AD. Therefore, ZBI is a more appropriate tool

	for assessing carer QoL in AD than EQ-5D. As such, although EQ-5D utilities are used for caregivers in the analysis to align with the NICE reference case, these are likely to underestimate the true benefit of lecanemab to caregivers. In addition, the direct evidence of a caregiver QoL benefit for lecanemab based on ZBI substantiates the company's concerns that the utility decrement approach, through which only [redacted] is estimated compared with excluding caregiver utilities entirely, is not consistent with patients' and carers' preferences. Finally, the model conservatively assumes just one caregiver per patient, which may further underestimate the benefits of lecanemab to caregivers; as emphasised in the 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".* By only considering the effects of lecanemab on one caregiver, the caregiver QALY benefit associated with lecanemab is likely further underestimated.
10	**Infusion cost (draft guidance 3.17)** To address the committee's request for further information regarding the estimated cost of lecanemab infusion, including a breakdown of expected resource use and exploration of alternatives, the company conducted the following activities: • Sought additional clinical expert opinion on the appropriate infusion cost for lecanemab • Conducted a hand search of administration costs used for other monoclonal antibodies in previous NICE technology appraisals (TAs) • Conducted a micro-costing study on the healthcare professional time taken for tasks related to administration of lecanemab. ***Clinical expert opinion*** As described in the CS (B.3.5.2.1.1), there is no NHS reference cost (HRG code) for the intravenous (IV) infusion of a monoclonal antibody therapy for AD, therefore the company sought clinical expert opinion in a UK HTA advisory board (July 2023) to establish the most appropriate proxy.[28] The administration cost for lecanemab was therefore assumed to be £207.59 per infusion, based on the average cost of a simple parenteral chemotherapy infusion [National Schedule of NHS Costs 2021/22 (SB12Z Simple parenteral chemotherapy at first attendance)].[29] NHS England suggested an alternative HRG code, WD02Z (Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider, Day case) during this appraisal, at a cost per infusion of £565, however this was withdrawn from the national tariff in 2020/21. In response to the committee's request for further information to fully explain the estimated costs, the company obtained additional clinical expert opinion in July 2024 on the appropriateness of HRG codes SB12Z and WD02Z as proxy administration costs for lecanemab. Two of the three clinicians agreed that chemotherapy was an appropriate proxy, whilst none believed that WD02Z was appropriate.[11] ***Hand-search for administration costs used in NICE TAs for monoclonal antibodies***

	To further assess the appropriateness of HRG codes SB12Z and WD02Z and identify alternative proxies for lecanemab, a hand search was conducted to review NICE TAs of monoclonal antibodies administered via IV infusion published over the last six years (2018-2024). The following appraisals were identified across various indications: TA897, TA585, TA862, TA540, TA763, and TA798.[30–35] The costs, infusion times, and assumptions for each HRG code (as outlined in the NHS Payment Scheme Annex B: Guidance on Currencies) used for administration in the committee's preferred assumptions in each appraisal, are detailed in Appendix A.2.6, Table 45. HRG code SB12Z was used in three of the appraisals (TA798, TA862, and TA540). Durvalumab for NSCLC (TA798) has an equivalent infusion duration to lecanemab (60 minutes), and trastuzumab deruxtecan for breast cancer (TA862) has a longer infusion duration than lecanemab at 90 minutes. However, the committee and EAG accepted SB12Z in all three appraisals. Two appraisals (TA763 and TA897) had varying infusion times for initial and subsequent infusions. Daratumumab for multiple myeloma (TA763 and TA897) has substantially longer infusions than lecanemab (7, 4, and 3 hours for first, second, and subsequent infusions, respectively), yet daratumumab administration costs in both appraisals (SB14Z in TA763: £385 and SB15Z in TA897: £471) were lower than NHS England's proposed cost for lecanemab (WD02Z; £565).[31,34] The company therefore believe that adopting an administration cost for lecanemab (60 minutes infusion) equal to or higher than those accepted in previous NICE appraisals for daratumumab (3-7 hours infusion) lacks credibility and therefore should not be used for decision-making. In the remaining appraisal for multiple sclerosis (TA585), ocrelizumab has an infusion time of 2.5-3.5 hours, and used HRG code AA30F (Medical care of patients with multiple sclerosis, with CC score 0-1, day case) for the administration cost, at £532.[35] Moreover, while the company acknowledge that multiple sclerosis was suggested as an alternative proxy in the first appraisal committee meeting for lecanemab, clinical feedback in July 2024 highlighted that intravenous infusions for multiple sclerosis require blood to be drawn prior to treatment to check for lymphocytes, neutrophils, liver function tests, and other relevant markers to ensure the patient's safety before proceeding with the infusion, which is not required for lecanemab. Therefore, the company do not believe AA30F is an appropriate proxy for lecanemab, due to the ocrelizumab infusion duration (2.5-3.5 hours) and the need for blood to be drawn prior to infusion. ***Micro-costing of lecanemab infusions based on UK clinical trial experience*** To address the committee's request for a breakdown of resource use for the administration of lecanemab, the company conducted a micro-costing exercise to estimate the time and staff resource needed to administer lecanemab in NHS practice. Through a hand search using the terms 'time and motion study', 'infusion', 'monoclonal antibody', and 'UK', the company identified Burcombe *et al.* (2013), a UK time and motion study of trastuzumab for treatment of patients with HER-2 positive early breast cancer. In this study, the mean active healthcare professional (HCP) time and costs associated with IV infusion of trastuzumab were quantified.[36] The company presented this information reported by Burcombe *et al.* to three HCPs (clinician, nurse, and pharmacist) who had clinical trial experience with lecanemab and asked them to update the tasks and HCP time accordingly to reflect expected lecanemab infusions in NHS practice. The mean time for each task was then calculated from the responses, and the corresponding costs were obtained from the PSSRU Unit Costs of Health and

	Social Care programme (2022-2027).[37] In addition, the consumables required for IV infusion were informed by Burcombe et al., inflated to 2023 values using the PSSRU inflation indices.[38] The mean active HCP time for each of the tasks from the micro-costing exercise was subsequently validated with another clinical expert with clinical trial experience with lecanemab. An average of the four responses was then used to generate the cost used in the base case. Full details of the micro-costing can be found in Appendix A.2.8, Tables 47-51. The infusion cost estimated by the micro-costing is £[redacted], which is lower than SB12Z and substantially lower than WD02Z. This implies that SB12Z is a conservative estimate of the cost of administering lecanemab. Therefore, in 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 adopted this micro-costing estimate in the base case, as it believes it is an accurate, comprehensive reflection of the time and staff resource that will be required to infuse lecanemab in NHS practice, based on UK clinical trial experience.
11	**Private care costs (draft guidance 3.18)** In light of the committee's request for further justification for the appropriate proportion of non-medical costs assumed be for private care, the company sought clarification from the authors of the Alzheimer's Society UK report on the proportion of costs that are private, but unfortunately could not obtain a response. The company would like to reiterate that the estimate of two thirds of non-medical costs being borne privately, suggested by the EAG, is based on an estimate from an Alzheimer's Society blog of 63% of all dementia costs being borne privately, hence is inclusive of societal costs, which are outside the NHS and PSS perspective and therefore the scope of this appraisal.[39] Therefore, the company does not consider this to appropriate. However, to explore this further, the company has used this figure to estimate the proportion of non-medical costs borne privately. The total dementia costs reported in the Alzheimer's Society Dementia UK update, inclusive of medical, non-medical, unpaid care, and other costs, is £26,316 (Table 5.3 of the Alzheimer's Society report).[40] The proportion of this borne privately (63%, based on the Alzheimer's Society blog) is £16,579.[39] Subtracting other private costs from this [i.e., unpaid care costs (£11,620) and 'other' costs (£111, assumed to be private)] leaves £4,848, representing the amount of non-medical costs borne privately, equating to 47.2% (=4,848/10,271). A scenario is therefore presented in which non-medical health state costs are reduced by 47.2%. This scenario yield an [redacted] in the ICER of £[redacted] (Appendix A.2.2.2.3).
12	**Severity (draft guidance 3.20)** The company thank the committee for highlighting the significant impact AD has on patients and their carers. As acknowledged in the original CS, lecanemab does not meet the threshold for the severity modifier due to the age of the early AD population and the chronic nature of the condition, despite AD being the leading cause of death in the UK in 2022. This is consistent with recent data published by ABPI through its review of the implementation in practice of the NICE Health Technology Evaluation Manual; this found that 80% of topics have received no QALY weighting since implementation of the severity modifier, compared with 61%

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	estimated by NICE prior to implementation.[41] This highlights the difficulty in meeting the absolute and proportional shortfall thresholds, suggesting the current methodology may not reflect societal preferences.[42] The company is aware discussions are ongoing regarding implementation and operation of the severity modifier, including by the NICE Board at its public Board meeting on 25th September 2024 at which it concluded the severity modifier is working as intended. Whilst the company acknowledges the committee's conclusion that it should not apply a greater weight to QALYs based on the severity modifier, the company believe that the numerous uncaptured benefits of lecanemab detailed in the draft guidance must be considered in decision-making. AD presents a uniquely complex and widespread burden that falls outside of the current QALY framework, through strain on caregivers and families' health, finances, and productivity.[43] As detailed in the CS (B.1.3.4.2, B.3.4.4.2, and B.3.13), the impact of AD on carers is wide-ranging, and some components of caregiver QoL and wellbeing are not captured within the QALY calculation, such as behavioural changes in the patient, which are particularly disturbing for caregivers, as highlighted in the ARUK patient organisation submission. Other considerations include development of mental health problems, strained family relationships, and the complex stages of grief experienced by a caregiver of someone with AD.[44,45] Therefore, given the expected underestimation of the effect of lecanemab on caregiver burden in the economic model due to reliance on EQ-5D and the methodological challenges cited in comment 9 regarding modelling of caregiver quality of life, the company believe it is critical for these to be considered in decision-making.
13	**Managed access (draft guidance 3.24)** [redacted] [redacted][46] [redacted]

Insert extra rows as needed

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Draft guidance response – appendix

September 2024

File name	Version	Contains confidential information	Date
[ID4043]_Lecanemab_DG_appendix_30Sept2024_CON_FINAL	1.0	Y	30th September 2024

A.1 Clinical data

Marketing authorisation for lecanemab was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) on 22nd August 2024. Lecanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε4 (*APOE4*) heterozygotes or non-carriers.[1] Results for primary, secondary, safety, and key exploratory endpoints from the Clarity AD core study in the approved indication are presented below. In addition, 36-month data from the open label extension (OLE) phase are presented for primary and safety endpoints.

For a detailed description of each primary and secondary outcome presented in this section, refer to the company submission, Document B2, Section B.2.3.1.1, Table 9.

A.1.1 Clarity AD core study

A.1.1.1 Clinical effectiveness results – ITT excluding *APOE4* homozygotes

A.1.1.1.1 Primary efficacy outcome: CDR-SB

Lecanemab showed [redacted] versus placebo across all six Clinical Dementia Rating–Sum of Boxes (CDR-SB) domains (Memory: *p*<[redacted]; Orientation: *p*<[redacted]; Judgement/Problem Solving: *p*< [redacted]; Community Affairs: *p*< [redacted]; Home and Hobbies: *p*< [redacted]; Personal Care: *p*< [redacted]), demonstrating that lecanemab provides manifold benefits to patients by 18 months (Table 1).

Table 1: Adjusted mean difference versus placebo in CDR-SB by domain

Domain		**Lecanemab (n=723)**	**Placebo (n=743)**
Week 79, n		[redacted]	[redacted]
Memory	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	

Orientation	Adjusted mean (SE)	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]
	95% CI	[redacted]
	P-value	[redacted]
	% difference vs placebo	[redacted]
Judgement problem solving	Adjusted mean (SE)	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]
	95% CI	[redacted]
	P-value	[redacted]
	% difference vs placebo	[redacted]
Community affairs	Adjusted mean (SE)	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]
	95% CI	[redacted]
	P-value	[redacted]
	% difference vs placebo	[redacted]
Home and hobbies	Adjusted mean (SE)	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]
	95% CI	[redacted]
	P-value	[redacted]
	% difference vs placebo	[redacted]
Personal care	Adjusted mean (SE)	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]
	95% CI	[redacted]
	P-value	[redacted]
	% difference vs placebo	[redacted]

Abbreviations: CDR-SB – Clinical Dementia Rating–Sum of Boxes; CI – confidence interval; SE – Standard error.

The adjusted mean treatment difference for lecanemab compared to placebo at 18 months across all domains of -0.579 (1.151 for lecanemab versus 1.730 for placebo) was highly statistically significant (p= <0.00001), reflecting 33% less decline in the CDR-SB (Table 2).

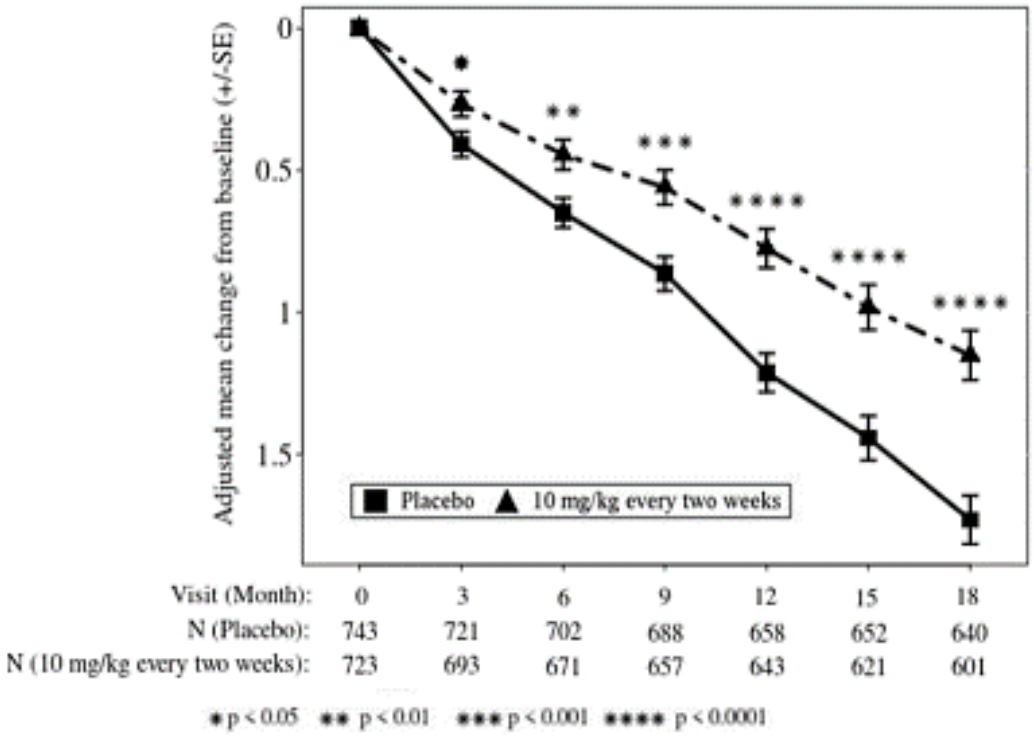
Table 2: Change from baseline in CDR-SB Score at 18 Months – MMRM

Statistic	Lecanemab (n= 723)	Placebo (n= 743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]
Adjusted mean (SE)	1.151 [redacted]	1.730 [redacted]
Adjusted mean difference (lecanemab – placebo)	-0.579	
95% confidence interval (CI) for differences	-0.811, -0.347	
p-value	<0.00001	
% Difference vs. placebo	-33%	

Source: Lecanemab MHRA SmPC, 2024[1]
Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating–Sum of Boxes; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Lecanemab showed statistically significant differences in CDR-SB scores from as early as three months, compared to placebo ($p< 0.05$). The absolute difference in CDR-SB scores between lecanemab and placebo continued to increase over time, with highly statistically significant changes (all $p<0.00001$) at 12, 15, and 18 months (Figure 1).

Figure 1: Adjusted mean change (±SE) from baseline in CDR-SB



Source: Lecanemab MHRA SmPC, 2024[1]

Abbreviations: CDR-SB – Clinical Dementia Rating – Sum of Boxes; kg – kilogram; mg – milligram; SE – standard error

Additionally, slope analysis suggested that continued improvement would be seen with longer treatment, with increasing separation over time translating to a [redacted] month delay in disease-related progression at 18 months increasing to an estimated [redacted] month delay at 27.3 months, based on CDR-SB (Figure 2). As a result, patients maintain independence and functionality for longer, improving both patient and carer QoL (CS, Document B, Section B.2.6.5).[2]

Figure 2: Slope analysis of rate of change over time of CDR-SB

Source: Eisai, data on file
Abbreviations: CDR-SB – Clinical Dementia Rating – Sum of Boxes; M – months.

A.1.1.1.2 Secondary efficacy outcomes

All key secondary endpoints including cognition, function, and biomarker changes (change from baseline at 18 months in amyloid PET Centiloids, 14-item Alzheimer's Disease Assessment Scale – Cognitive subscale [ADAS-Cog14], Alzheimer's disease composite score [ADCOMS], and Activities of Daily Living Scale for use in Mild Cognitive Impairment [ADCS MCI-ADL]) yielded highly statistically significant results favouring lecanemab compared with placebo. For all these secondary endpoints, separation emerged at the first timepoint (three months for amyloid PET using Centiloids, ADAS-Cog14 and ADCOMS, six months for ADCS MCI-ADL);

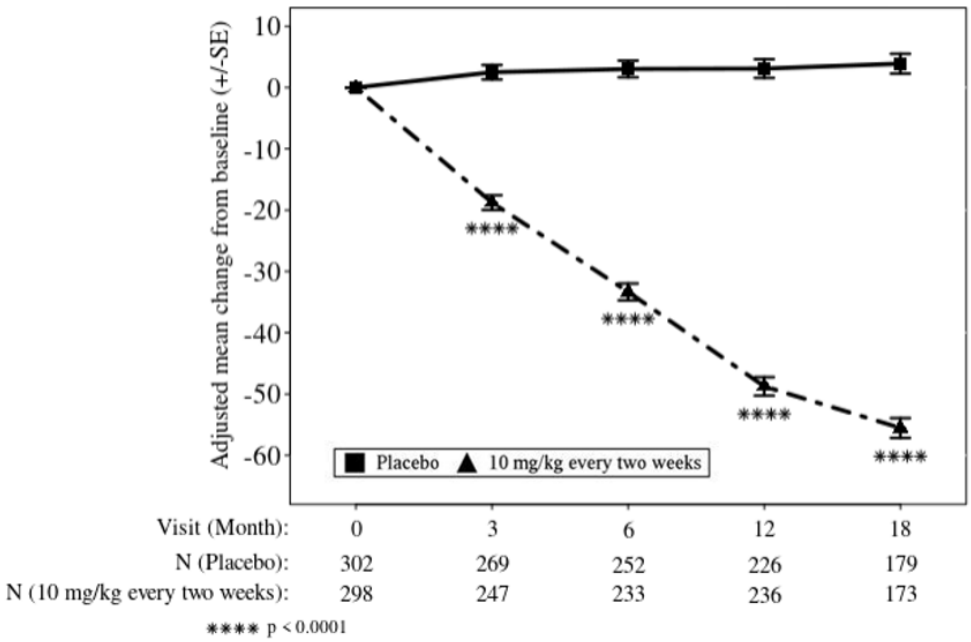
statistically significant differences were observed for all endpoints by six months (p<0.05); and highly significant differences were observed beyond six months for all endpoints (p<0.001).

A.1.1.1.2.1 Amyloid PET using Centiloids

For a description of the measure of amyloid positron emission tomography (PET) using Centiloids, see Section B.2.6.2.1 in the company submission.

In Clarity AD, the baseline level in the lecanemab group was [redacted] Centiloids, reducing to [redacted] Centiloids at 18 months, a [redacted]% Centiloid decrease. This is below the threshold for amyloid negativity of approximately 30 Centiloids which is considered a 'normal' level, above which participants are considered to have elevated or 'higher than normal' brain amyloid.[3] In contrast, the baseline level in the placebo group was [redacted] Centiloids, increasing to [redacted] Centiloids at 18 months, a [redacted]% Centiloid increase. A highly statistically significant change from baseline was observed, starting as early as three months, through to 18 months (p<0.0001).

Figure 3: Adjusted mean change (±SE) from baseline in Centiloid



Source: Lecanemab MHRA SmPC, 2024[1]
Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating – Sum of Boxes; kg – kilogram; mg – milligram; SE – standard error

A.1.1.1.2.2 Patients converting to amyloid negativity

There was a [redacted] between lecanemab and placebo in the proportion of patients who converted to amyloid negativity by Centiloids, with a significant difference being seen as early as three months (lecanemab [redacted]% vs placebo [redacted]%, *p*= [redacted], Figure 4). This difference was maintained through to 18 months of treatment, with a highly statistically significant difference seen from six months. Only [redacted]% of patients receiving placebo had achieved amyloid negativity at 18 months compared to [redacted]% of patients who received lecanemab (*p*< [redacted]).

Figure 4: Proportion of patients who became amyloid negative by visit – PD analysis set excluding *APOE4* homozygotes

Source: Eisai, data on file, table 14.2.7.1.5nh
Abbreviations: PET – positron emission tomography; SE – standard error.
Amyloid status was based on amyloid PET using Centiloids. Amyloid PET using Centiloids ≥30 is considered as amyloid positive. Only patients who enrolled in the amyloid PET substudy and were amyloid positive at baseline were included.

A.1.1.1.2.3 ADAS-Cog14

A description of ADAS-Cog14 can be found in the company submission, Section B.2.6.2.3.

The adjusted mean difference for lecanemab compared to placebo at 18 months (-1.633) was highly statistically significant, equating to 28% less decline in ADAS-Cog14 (*p*= 0.00052) (Table 3). Starting as early as six months, lecanemab showed

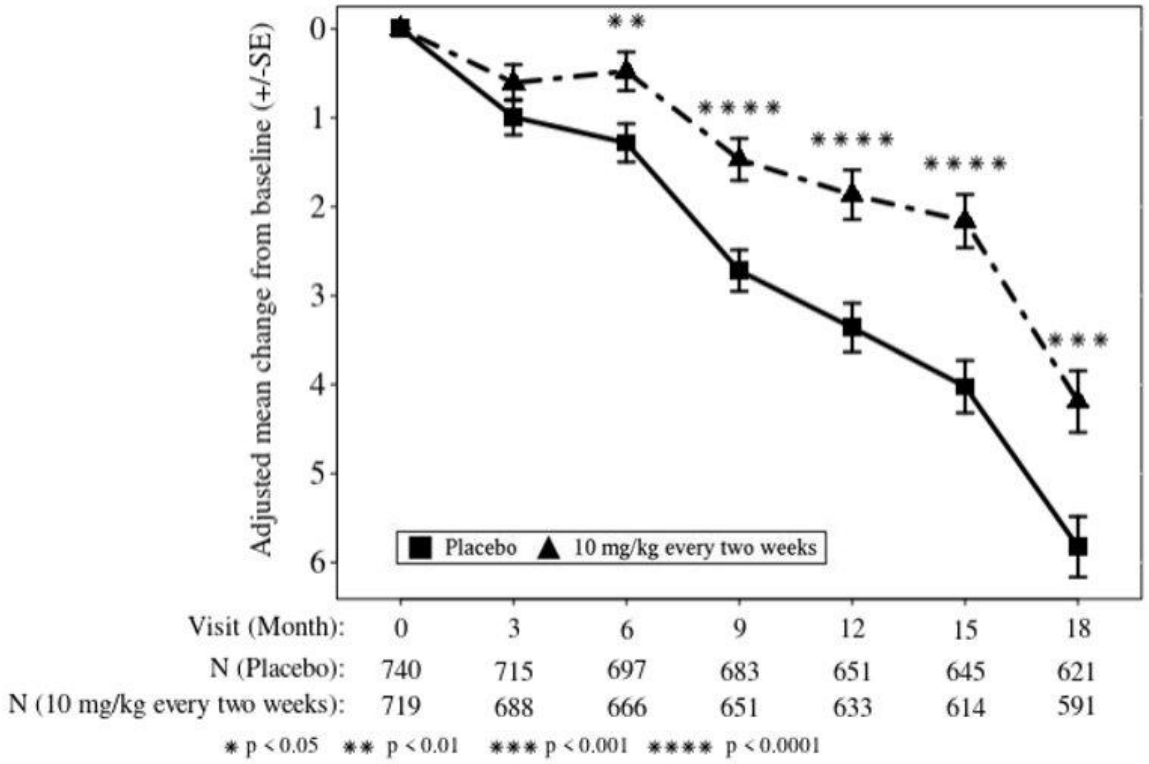
statistically significant (p<0.01) changes from baseline compared to placebo, which was maintained up to 18 months (p<0.001) (Figure 5). The absolute treatment difference also tended to increase over time.

Table 3: Statistical analysis of change from baseline in ADAS-Cog14 at 18 months – MMRM, Core study

Statistic	Lecanemab (n=723)	Placebo (n= 743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	4.211 [redacted]	5.845 [redacted]
Adjusted mean difference (lecanemab – placebo)	-1.633	
95% CI for differences	-2.555, -0.712	
p-value	0.00052	
% Difference vs. placebo	-28%	

Source: Lecanemab MHRA SmPC, 2024[1]
Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive subscale 14-item version; CI – Confidence interval; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Figure 5: Change from baseline in ADAS-Cog14 at interim timepoints



Source: Lecanemab MHRA SmPC, 2024[1]
Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version; kg – kilogram; Lec – Lecanemab; mg – milligram; SE – standard error

A.1.1.1.2.4 ADCOMS

The adjusted mean difference for lecanemab compared to placebo at 18 months [redacted]) was [redacted] on change from baseline ADCOMS, equating to [redacted]% less decline (*p*= [redacted]) (Table 4 and Figure 6). A [redacted] ([redacted] (*p*< [redacted]) was observed [redacted] [redacted] [redacted] (*p*< [redacted]) from 9 months onwards. The absolute treatment difference also tended to increase over time.

Table 4: Statistical analysis of change from baseline in ADCOMS – MMRM – week 79

Statistic	**Lecanemab (n= 723)**	**Placebo (n= 743)**
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file
Abbreviations: ADCOMS – Alzheimer's Disease Composite Score, CI – Confidence interval; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Figure 6: Change from baseline in ADCOMS

Source: Eisai, data on file
** *p*<0.01, *** *p*<0.001, **** *p*<0.0001, ***** *p*<0.00001.
Abbreviations: AD – Alzheimer's disease; ADCOMS – Alzheimer's Disease Composite Score; kg – kilogram; Lec – Lecanemab; mg – milligram; MMRM – mixed model for repeated measures; SE – standard error.

A.1.1.1.2.5 ADCS MCI-ADL

See Section B.2.6.2.5 of the company submission for a full description of ADCS MCI-ADL.

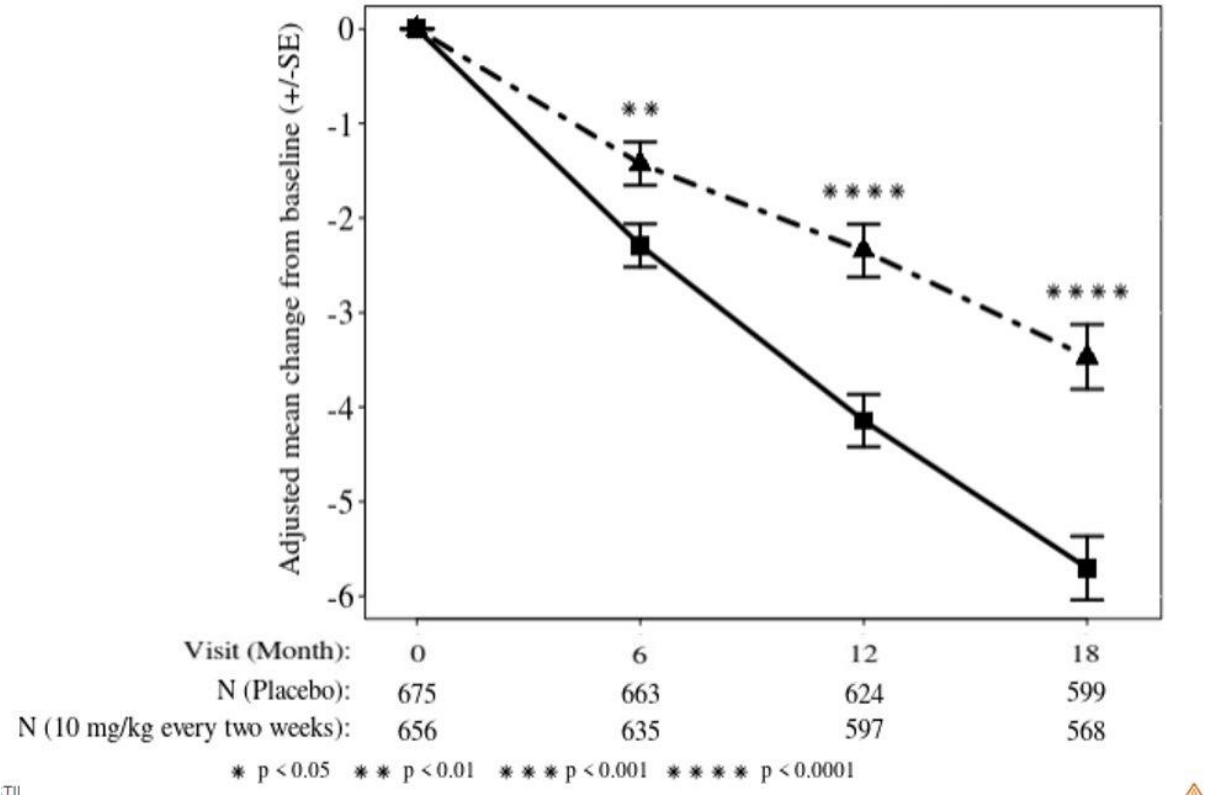
The adjusted mean treatment difference for lecanemab compared to placebo at 18 months (2.234) was highly statistically significant, equating to 39% less decline in ADCS MCI-ADL (*p*<0.00001) (Table 5). At six months, the earliest assessment timepoint, lecanemab showed statistically significant changes (*p*<0.01) in ADCS MCI-ADL from baseline compared to placebo (Figure 7). At 12 and 18 months, lecanemab showed highly statistically significant changes in ADCS MCI-ADL from baseline compared to placebo (both *p*<0.0001). The absolute treatment difference also tended to increase over time.

Table 5: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM

Statistic	Lecanemab (n= 723)	Placebo (n= 743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	-3.469 [redacted]	-5.703 [redacted]
Adjusted mean difference (lecanemab – placebo)	2.234	
95% CI for differences	1.342, 3.126	
p-value	<0.00001	
% Difference vs. placebo	-39%	

Source: Lecanemab MHRA SmPC, 2024[1]
Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CI – Confidence interval; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Figure 7: Change from baseline in ADCS MCI-ADL at interim timepoints



Source: Lecanemab MHRA SmPC, 2024[1]
Abbreviations: AD – Alzheimer's disease; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; kg – kilogram; Lec – Lecanemab; mg – milligram; SE – standard error

A.1.1.1.2.6 Key exploratory endpoint: Time to worsening of Global CDR score at 18 months

See Section B.2.6.4 of the company submission for a full description of time to worsening of global CDR score.

At 18 months, lecanemab showed a statistically significant reduction in the risk of progression to the next stage of AD on the global CDR score (hazard ratio = [redacted], 95% CI [redacted], *p*=[redacted]) (Figure 8). This delay in progression to more severe AD health states means that patients receiving lecanemab remain at home in their community and independent when completing ADLs for longer, which may delay or reduce residential care placement.[4]

Figure 8: Time to worsening Global CDR score at 18 months

Source: Eisai, data on file
Abbreviations: CDR – Clinical Dementia Rating; CI – confidence interval.

A.1.1.2 Health related quality of life

An introduction to health-related quality of life (HRQoL), the types of HRQoL measured in Clarity AD, and the importance of considering patient-by-proxy QoL in AD are detailed in Section B.2.6.5 in the company submission.

A.1.1.2.1 EQ-5D-5L

A.1.1.2.1.1 Patient reported

The adjusted mean difference for lecanemab compared to placebo in the Patient's Survey at 18 months ([redacted]) was [redacted], representing [redacted]% [redacted] decline (*p*=[redacted]).

Table 6: Statistical analysis of change from baseline in EQ-5D-5L, Health today (VAS subtotal) at 18 months, patient reported – MMRM

Statistic	Lecanemab (n=723)	Placebo (n=743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.4.2nh
Abbreviations: CI – Confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

A.1.1.2.1.2 Patient-by-proxy

The adjusted mean difference for lecanemab compared to placebo in the Patient-by-Proxy Survey at 18 months ([redacted]) equated to [redacted]% [redacted] decline, *p*=[redacted] (Table 7).

Table 7: Statistical analysis of change from baseline in EQ-5D-5L, Health today (VAS subtotal) at 18 months, patient-by-proxy – MMRM

Statistic	Lecanemab (n=723)	Placebo (n=743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.4.2nh
Abbreviations: CI – Confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

A.1.1.2.1.3 Study partner

The adjusted mean difference for lecanemab compared to placebo in the Partner's Survey ([redacted]) represented [redacted]% [redacted] decline, *p*=[redacted] (Table 8).

Table 8: Statistical analysis of change from baseline in EQ-5D-5L, Health today (VAS subtotal) at 18 months, Study partner – MMRM

Statistic	Lecanemab (n=723)	Placebo (n=743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.4.2nh
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

A.1.1.2.1.4 Committee request – EQ-5D-3L utility values

Mixed model for repeated measures (MMRM) were fitted to provide estimates of health state utility adjusted for factors that may influence the outcome in the modified population, these are: treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Therefore as covariates have been adjusted for, the adjusted mean change from baseline in EQ-5D-3L utility values, analysed using a MMRM, are presented in Table 9 and Figure 8 to Figure 10 below, rather than least-squares mean change as requested by the Committee in the draft guidance (Section 3.6).

The adjusted mean difference in EQ-5D-3L utility values for lecanemab compared to placebo for the Patient's Survey at 18 months ([redacted]) represents [redacted]% [redacted] decline compared to placebo. For the Patient-by-Proxy Survey, this difference ([redacted]) represents [redacted]% [redacted] decline compared to placebo. The difference for the Study Partner Survey ([redacted]) showed [redacted]% [redacted] decline compared to placebo. While both lecanemab and placebo saw increases from baseline for the Patient's Survey, lecanemab showed benefits compared with placebo across the Patient's Survey and Patient-by-Proxy Survey measurements.

Table 9: Adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM

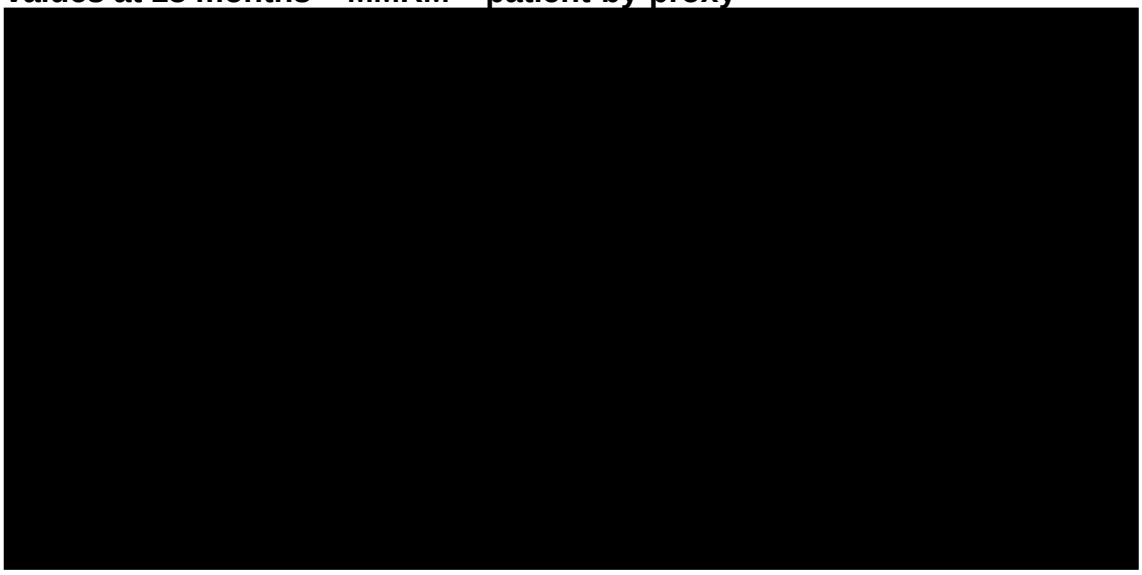
Sub-category		Lecanemab (N=723)	Placebo (N=743)
Patient reported	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Patient-by-Proxy	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Study partner	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.4.11nh
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

Figure 9: Plot of adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM – patient reported

Source: Eisai, data on file, figure 14.2.3.4.11.1nh
Abbreviations: MMRM – mixed model for repeated measures; SE – standard error.

Figure 10: Plot of adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM – patient-by-proxy



Source: Eisai, data on file, figure 14.2.3.4.11.1nh
Abbreviations: MMRM – mixed model for repeated measures; SE – standard error.

Figure 11: Plot of adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM – study partner

Source: Eisai, data on file, figure 14.2.3.4.11.1nh
Abbreviations: MMRM – mixed model for repeated measures; SE – standard error.

A.1.1.2.2 QOL-AD

A.1.1.2.2.1 Patient reported

The adjusted mean difference for lecanemab compared to placebo in the Patient's Survey at 18 months ( ) was , representing % decline, *p*= (Table 10)

Table 10: Statistical analysis of change from baseline in QOL-AD at 18 months, Patient-reported – MMRM

Statistic	Lecanemab (n=723)	Placebo (n=743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.5.2nh
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

A.1.1.2.2.2 Patient-by-Proxy

The adjusted mean difference for lecanemab compared to placebo in the Patient-by-Proxy Survey ([redacted]) represented [redacted]% [redacted] decline, *p*=[redacted] (Table 11).

Table 11: Statistical analysis of change from baseline in QOL-AD at 18 months, Partner as proxy – MMRM

Statistic	Lecanemab (n=723)	Placebo (n=743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.5.2nh
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

A.1.1.2.3 Zarit's Burden Interview

The adjusted mean difference between lecanemab compared to placebo at 18 months ([redacted]) was [redacted], equating to [redacted]% [redacted] decline, *p*=[redacted] (Table 12).

Table 12: Statistical analysis of change from baseline in ZBI at 18 months, Partner as proxy – MMRM

Statistic	Lecanemab (n=723)	Placebo (n=743)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Eisai, data on file, Table 14.2.3.6.2nh
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error; ZBI – Zarit's Burden Interview

A.1.1.3 Adverse reactions

A.1.1.3.1 AEs overview

A summary of adverse events (AEs) that occurred in Clarity AD is presented in Table 13. The overall incidence of treatment-emergent adverse events (TEAEs) was similar between lecanemab ([redacted]) and placebo [redacted] (Table 13). The most common adverse reactions were infusion-related reaction (26%), ARIA-H (13%), fall (11%), headache (11%) and ARIA-E (9%).[1]

Table 13: Adverse event overview, core study (Clarity AD, SAS excluding *APOE4* homozygotes)

Category	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
TEAEs	[redacted]	[redacted]
Treatment-related TEAEs[a]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]
Deaths[b]	[redacted]	[redacted]
Other SAEs[c]	[redacted]	[redacted]
Life threatening	[redacted]	[redacted]
Requires inpatient hospitalisation or prolongation of existing hospitalisation	[redacted]	[redacted]
Persistent or significant disability or incapacity	[redacted]	[redacted]
Congenital anomaly/birth defect	[redacted]	[redacted]
Important medical events	[redacted]	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]	[redacted]
TEAEs leading to study drug withdrawal	[redacted]	[redacted]
TEAEs leading to study drug dose interruption	[redacted]	[redacted]
TEAEs leading to infusion interruption	[redacted]	[redacted]
TEAEs of special interest	[redacted]	[redacted]

Source: Eisai, data on file, Table 14.3.1.2.1
Abbreviations: AE – adverse event; MedDRA – Medical Dictionary for Regulatory Activities; n – number of patients in treatment group; SAE – serious adverse event; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse event.
A: Includes TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality.
B: Includes all patients with SAE resulting in death.
C: Includes patients with nonfatal SAEs only. If a patient had both fatal and nonfatal SAEs, the patient is counted in the previous fatal row and is not counted in the nonfatal row.

A.1.1.3.2 Adverse events of special interest

Infusion-related reactions, skin rash, other hypersensitivity reactions, ARIA-E, and ARIA-H occurred at a higher incidence in the lecanemab arm ([redacted]) than the placebo arm ([redacted]) (Table 14).

AESI data for the indicated population required for the economic model (ARIA-E, isolated ARIA-H and infusion-related reactions) are reported in further detail in below sections.

Table 14: Treatment-emergent adverse events of special interest, core (Clarity AD, SAS excluding *APOE4* homozygotes)

Preferred term	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
Patients with any TEAE of special interest	[redacted]	[redacted]
ARIA-E	67 (8.9)	10 (1.3)
ARIA-H	98 (12.9)	52 (6.8)
Macrohaemorrhage	[redacted]	[redacted]
Superficial siderosis	[redacted]	[redacted]
Cerebral microhaemorrhage	[redacted]	[redacted]
Infusion-related reactions	[redacted]	[redacted]
Skin rash	[redacted]	[redacted]
Other hypersensitivity	[redacted]	[redacted]
Suicidal behaviour	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]

Source: Eisai, data on file, Table 14.3.2.6.1
Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse events.

A.1.1.3.2.1 ARIA-E

Of the patients with ARIA-E, most treatment-emergent ARIA-E were radiographically mild (lecanemab: [redacted]) or moderate (lecanemab: [redacted]) in severity. There was [redacted] categorised as having radiographically severe ARIA-E in the lecanemab arm and no patients in the placebo arm (Table 15). The rate of symptomatic ARIA-E was [redacted]% in the lecanemab arm. Most treatment-emergent ARIA-E in the lecanemab arm were asymptomatic ([redacted]), whilst all ARIA-E were asymptomatic in the placebo arm.

Table 15: Treatment-emergent ARIA-E by maximum radiographic severity

ARIA term Maximum radiographic severity	Number of patients, n (% of total population)	
	Lecanemab (n=757)	Placebo (n=764)
Any ARIA-E	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Symptomatic ARIA-E	[redacted]	[redacted]
Asymptomatic ARIA-E	[redacted]	[redacted]

Source: Eisai, data on file. Table 14.3.2.6.17
Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; n – number of patients in treatment group.

A.1.1.3.2.2 Isolated ARIA-H

Isolated ARIA-H events were similar between lecanemab ([redacted]) and placebo ([redacted]) overall and by maximum radiographic severity (Table 16). Of the patients with isolated ARIA-H, most treatment-emergent isolated ARIA-H were radiographically mild (lecanemab: [redacted]. There were [redacted] categorised as having radiographically moderate isolated ARIA-H and [redacted] categorised as having radiographically severe isolated ARIA-H in the lecanemab arm. [redacted] was categorised as having radiographically moderate isolated ARIA-H and [redacted] had radiographically severe isolated ARIA-H in the placebo arm (Table 16).

Table 16: Treatment-emergent isolated ARIA-H by maximum radiographic severity

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
Subjects with ARIA-H	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Eisai, data on file. Table 14.3.2.6.10nh
Abbreviations: ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group.
ARIA-H is defined as events of superficial siderosis or cerebral microhaemorrhage.

Please note that the definition for ARIA-H has changed since the original CS, as regulatory bodies have asked for macrohaemorrhages to be reported separately from the rest of ARIA-H. The previous definition of ARIA-H was microhaemorrhages [10 or less and >10], superficial siderosis, macrohaemorrhage; including asymptomatic ARIA-H and symptomatic ARIA-H. There were [redacted] macrohaemorrhage events, [redacted] in the lecanemab arm (maximum radiographic severity: [redacted]) and [redacted] event in the placebo arm.

A.1.1.3.2.3 Infusion-related reactions

Infusion-related reactions, which include the preferred terms 'infusion related reaction' and 'infusion site reaction', were reported for [redacted] lecanemab patients compared to [redacted] placebo patients (Table 17).

Most infusion-related reactions were mild or moderate in severity, with Grade 1 (lecanemab: [redacted] placebo: [redacted] and Grade 2 (lecanemab: [redacted] placebo: [redacted]. No patients in the placebo arm reported Grade 3 or 4 infusion-related reactions. In the lecanemab arm, [redacted] and [redacted] patients reported Grade 3 and Grade 4 infusion-related reactions, respectively. Per Clarity AD protocol, all [redacted] patients were discontinued from study treatment and did not receive subsequent infusions.

Table 17: Summary of infusion-related reactions by maximum grade

NCI-CTCAE Grade	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
Any grade	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Eisai, data on file. Table 14.3.2.6.4
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

A.1.2 Clarity AD OLE phase

A.1.2.1 Primary efficacy outcome: CDR-SB

Figure 12 shows the adjusted mean change from baseline in CDR-SB for early and delayed start patients receiving lecanemab versus patients observed in a matched cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. At 36 months, lecanemab showed an absolute treatment difference in CDR-SB of [redacted] in the early start group compared to ADNI. This supports that the CDR-SB efficacy at 18 months is maintained through 36 months as the absolute treatment difference between lecanemab and placebo continues to expand from 18 through 36 months.

Figure 12: Adjusted mean change (±SE) from baseline in CDR-SB (OLE)

Source: Eisai, data on file
Note: the delayed start group is the black line, which at 18 months changes to green to represent patients moving onto treatment with lecanemab.
Abbreviations: AD – Alzheimer's disease; ADNI – Alzheimer's Disease Neuroimaging Initiative; CDR-SB – Clinical Dementia Rating – Sum of Boxes; kg – kilogram; mg – milligram

A.1.2.2 AEs overview

The OLE Safety Analysis Set contains pooled data from the Core Study and OLE Phase in which subjects received lecanemab 10 mg/kg biweekly. Of the [redacted] subjects in the OLE Safety Analysis Set, [redacted] had at least

one TEAE by 36 months, the majority of which were mild or moderate and nonserious (Table 18). Severe TEAEs were reported for [redacted] patients by 36 months.

Table 18: Adverse event overview, OLE (Clarity AD, SAS excluding *APOE4* homozygotes)

Category	Number of patients, n (%)
	Lecanemab (n=[redacted])
TEAEs	[redacted]
Treatment-related TEAEs[a]	[redacted]
Severe TEAEs	[redacted]
Serious TEAEs	[redacted]
Deaths[b]	[redacted]
Other SAEs[c]	[redacted]
Life threatening	[redacted]
Requires inpatient hospitalisation or prolongation of existing hospitalisation	[redacted]
Persistent or significant disability or incapacity	[redacted]
Congenital anomaly/birth defect	[redacted]
Important medical events	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]
TEAEs leading to study drug withdrawal	[redacted]
TEAEs leading to study drug dose interruption	[redacted]
TEAEs leading to infusion interruption	[redacted]
TEAEs of special interest	[redacted]

Source: Eisai, data on file, Table 14.3.1.2.1nh
Abbreviations: AE – adverse event; MedDRA – Medical Dictionary for Regulatory Activities; n – number of patients in treatment group; OLE – Open label extension; SAE – serious adverse event; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse event.
Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received placebo in the Core Study, and is the Core Study baseline for subjects who received lecanemab 10 mg/kg Biweekly in the Core Study.
A: Includes TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality.
B: Includes all patients with SAE resulting in death.
C: Includes patients with nonfatal SAEs only. If a patient had both fatal and nonfatal SAEs, the patient is counted in the previous fatal row and is not counted in the nonfatal row.

Incidence of adverse events of special interest such as infusion-related reactions, skin rash, other hypersensitivity reactions, ARIA-E, and ARIA-H in the OLE Safety Analysis Set was [redacted].

Table 19: Treatment-emergent adverse events of special interest, OLE (Clarity AD, SAS excluding *APOE4* homozygotes)

Preferred term	Number of patients, n (%)
	Lecanemab (n=[redacted])
Patients with any TEAE of special interest	[redacted]
ARIA-E	[redacted]
ARIA-H	[redacted]
Macrohaemorrhage	[redacted]
Superficial siderosis	[redacted]
Cerebral microhaemorrhage	[redacted]
Infusion-related reactions	[redacted]
Skin rash	[redacted]
Other hypersensitivity	[redacted]
Suicidal behaviour	[redacted]
Suicidal ideation	[redacted]

Source: Eisai, data on file, Table 14.3.2.6nh
Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; OLE – Open label extension; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse events.

A.1.3 Committee requests

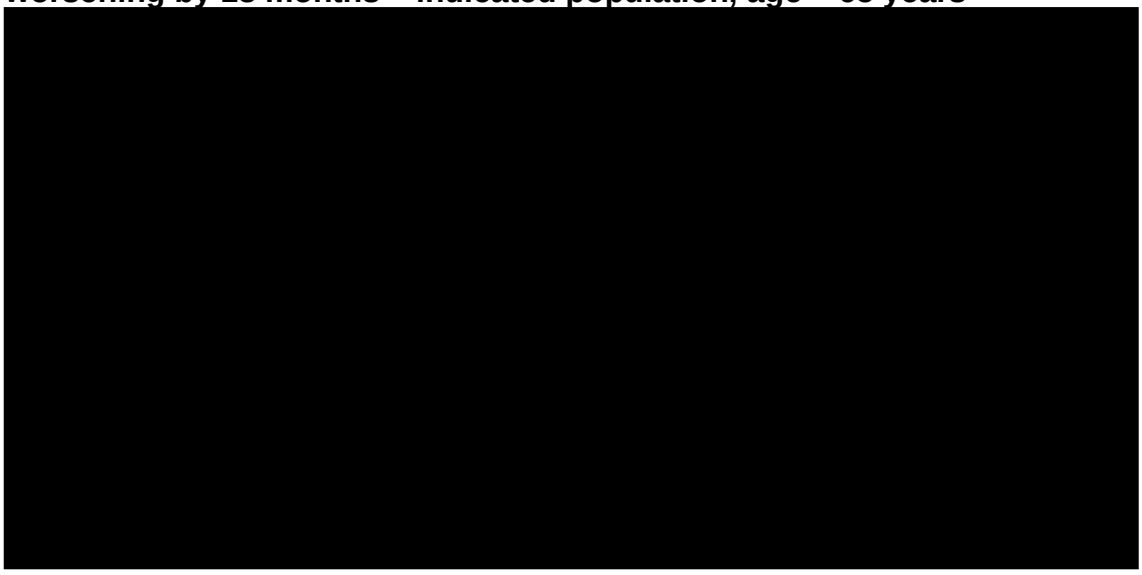
A.1.3.1 Distribution of the CDR-SB treatment effect for different subgroups

As described in the draft guidance response, section 3.9, the distribution of the CDR-SB treatment effect, overall and for age (<65 years, ≥65 to <75 years, ≥75 years) and *APOE4* (non-carrier and heterozygote) subgroups, are presented in Figure 13 to Figure 18.

Figure 13: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population

Abbreviations: *APOE4* – Apolipoprotein E4; CDR-SB – Clinical dementia rating – sum of boxes; ITT – intent-to-treat; RR – relative risk difference from placebo

Figure 14: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, age < 65 years



Abbreviations: CDR-SB – Clinical dementia rating – sum of boxes; RR – relative risk difference from placebo

Figure 15: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, age 65 to 75 years

Abbreviations: CDR-SB – Clinical dementia rating – sum of boxes; RR – relative risk difference from placebo

Figure 16: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months - indicated population, age ≥ 75 years

Abbreviations: CDR-SB – Clinical dementia rating – sum of boxes; RR – relative risk difference from placebo

Figure 17: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, *APOE4* non-carriers

Abbreviations: *APOE4* – Apolipoprotein E4; CDR-SB – Clinical dementia rating – sum of boxes; RR – relative risk difference from placebo

Figure 18: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, *APOE4* heterozygotes

Abbreviations: *APOE4* – Apolipoprotein E4; CDR-SB – Clinical dementia rating – sum of boxes; RR – relative risk difference from placebo

A.2 Economic data

A.2.1 Updated model inputs

As detailed in the draft guidance response, comment 2, the cost-effectiveness model inputs have been updated to reflect the indicated population (Table 20).

Table 20: Cost-effectiveness model inputs changed to reflect the indicated population

Variable			Value or reference to appropriate section in draft guidance response or CEM	Source
Clinical inputs	Baseline characteristics	Age (years)	[redacted]	Clarity AD, Eisai data on file
		Percentage female	[redacted]	
		Baseline proportion MCI due to AD	[redacted]	
		Baseline proportion mild AD	[redacted]	
		Mean weight (kg)	[redacted]	
		Distribution of patients across weight bands	'Wastage' sheet in CEM	
	Time to worsening hazard ratios	MCI due to AD (CDR-SB)	[redacted]	Clarity AD, Eisai data on file
		Mild AD (CDR-SB)	[redacted]	
		MCI due to AD (Global CDR)	[redacted]	
		Mild AD (Global CDR)	[redacted]	
	Patient counts at 0-18 months		'Patient counts' sheet in CEM	Clarity AD, Eisai data on file
	Multistate survival analysis (MSM)		Appendix A.2.3, 'Multistate' sheet in CEM	
	Discontinuation rate	MCI due to AD	[redacted]	Clarity AD, Eisai data on file
		Mild AD	[redacted]	
		Weighted (base case)	[redacted]	
	Adverse event rates		'Clinical data' sheet in CEM	Clarity AD, Eisai data on file
Quality of life inputs	Patient and carer health state utilities		Appendix A.2.4	Clarity AD MMRM, Eisai data on file

Variable			Value or reference to appropriate section in draft guidance response or CEM	Source
Cost inputs	Compliance		[redacted]%	Clarity AD, Eisai data on file
	APOE4 testing	Testing unit cost	[redacted]	NHSE BIA submission
		Outpatient appointment unit cost	[redacted]	
		Genetic counselling unit cost	[redacted]	

Abbreviations: AD – Alzheimer's disease; APOE4 – Apolipoprotein E4; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating – Sum of Boxes; CEM – cost-effectiveness model; kg – kilogram; MCI – mild cognitive impairment; MSM – multistate model; NHSE – National Health Service England.

A.2.2 Cost-effectiveness results

A.2.2.1 Updated base case results

Based on a [redacted] for lecanemab, the cost-effectiveness of lecanemab compared with SoC is £[redacted] per QALY gained (Table 21).

Table 21: Base-case results

Technology	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	(per QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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.2.2.1.1 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 22.

Table 22: Updated base case cost-effectiveness results (PAS price)

#	Assumption	ICER (individual change)*	ICER (cumulative change)
Company base case (as per addendum submitted 22nd April)		[redacted]	
1	Model inputs amended to reflect the indicated population (*APOE4* non-carriers and heterozygotes)**	[redacted]	[redacted]
2	Removal of serious AEs	[redacted]	[redacted]
3	Baseline proportion of patients with MCI due to AD and mild AD aligned with EAG preference, and weighted discontinuation rate applied†	[redacted]	[redacted]
4	Modelling approach: multistate survival model	[redacted]	[redacted]
5	Mortality HR for MCI due to AD: 0.63 (Crowell et al.)	[redacted]	[redacted]
6	Caregiver QoL modelled as utility increments	[redacted]	[redacted]
7	Inclusion of *APOE4* testing for all patients tested (including *APOE4* homozygotes)	[redacted]	[redacted]
8	Lecanemab administration cost source: micro-costing study	[redacted]	[redacted]

9	Revised PAS	[redacted]	[redacted]
Updated company base case		[redacted]	

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

*Individual ICER impact for changes 2 onwards are presented versus the indicated population ICER, as comparisons versus the ITT population including APOE homozygotes are no longer relevant.

**For a full list of model inputs updated to reflect the indicated population please see Comment 2 in the draft guidance response.

†The discontinuation rate in the model was updated to reflect the weighted split between MCI due to AD and mild AD.

A.2.2.2 Sensitivity analyses results

A.2.2.2.1 Probabilistic sensitivity analysis

The mean costs and QALYs in the probabilistic sensitivity analysis were comparable to the deterministic base case values, resulting in a probabilistic ICER just £35 higher than the base case ICER (£[redacted] per QALY, Table 23). The incremental cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 19 and Figure 20, respectively.

Table 23: PSA base-case results

Technology	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (per QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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 19: Incremental cost-effectiveness plane

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

Figure 20: Cost-effectiveness acceptability curve

Abbreviations: SoC - standard of care

A.2.2.2.2 One-way sensitivity analyses

A one-way sensitivity analysis (OWSA) tornado diagram presenting the top ten most sensitive parameters is presented in Figure 21 with tabulated results presented in Table 24.

Table 24: Tabulated OWSA results for lecanemab vs SoC

Parameter	Lower bound ICER	Upper bound ICER	Difference
Time to worsening HR, mild AD (CDR-SB)			
Utility: Farina (carer as proxy) - Mild AD			
Time to worsening HR, MCI due to AD (CDR-SB)			
Utility: Farina (carer as proxy) - Severe AD			
Lecanemab compliance			
Utility: Farina (carer as proxy) - Moderate AD			
Farina caregiver institution decrement			
Mortality rate: Crowell - severe AD			
Caregiver utility: Black - community - Severe AD			
Lecanemab cost of administration (micro-costing)			

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

Figure 21: OWSA tornado diagram

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.2.2.2.3 Scenario analyses

Table 25: Scenario analysis results

#	Scenario	ICER
	Base case	[redacted]
1.	1.5% discounting for costs and outcomes	[redacted]
2.	3.5% discount for costs, 1.5% discount for outcomes	[redacted]
3.	Baseline age: 65	[redacted]
4.	Baseline age: 60	[redacted]
5.	Health states defined by global CDR	[redacted]
6.	Diagnostic testing excluded (*APOE4* and amyloid)	[redacted]
7.	Drug wastage excluded	[redacted]
8.	Caregiver utility method: patient and care additive	[redacted]
9.	MCI due to AD only	[redacted]
10.	Mild AD only	[redacted]
11.	MCI due to AD only + aged 60 years at baseline	[redacted]
12.	NHSE cost inputs	[redacted]
13.	Trial based treatment duration scenario	[redacted]
14.	Administration cost: SB12Z	[redacted]
15.	AE disutilities excluded	[redacted]
16.	MMRM-derived utilities (self-reported for patients)	[redacted]
17.	Reduce non-medical health state costs by 47.2%	[redacted]
18.	Multistate model (0-18 months core, 18-36 months OLE) T1-T3: Weibull, T4: exponential	[redacted]
19.	Multistate model (0-18 months core: T1-T3: Weibull, T4: exponential; 18-36 months OLE: T1-T2: Weibull, T3-T4: Gompertz)	[redacted]
20.	Multistate model (0-18 months core: T1-T3: Weibull, T4: exponential; 18-36 months OLE: T1-T2: Weibull, T3: Gompertz, T4: exponential)	[redacted]
21.	Assume 10% patients remain on treatment in institution	[redacted]
22.	OLE discontinuation rate after 18 months	[redacted]
23.	Include quarterly outpatient appointments	[redacted]
24.	Treatment effect for moderate AD	[redacted]
25.	Apply treatment effect waning after all-cause discontinuation	[redacted]
26.	Treatment waning after all-cause discontinuation + treatment effect in moderate AD	[redacted]
27.	State transition model	[redacted]
28.	Clarity AD mortality for 0-18 months	[redacted]
29.	Mortality in MCI health state equal to general population	[redacted]

Abbreviations: AD – Alzheimer's Disease; CDR – Clinical dementia rating; HR – hazard ratio; MCI – mild cognitive impairment; MRI – magnetic resonance imaging.

A.2.2.3 Disaggregated results

Table 26: Disaggregated QALYs and LYs

Setting	Health state	Discounted			Undiscounted		
		SoC	Lecanemab	Incremental vs. SoC	SoC	Lecanemab	Incremental vs. SoC
QALYs							
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							
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							
	MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Setting	Health state	Discounted			Undiscounted		
		SoC	Lecanemab	Incremental vs. SoC	SoC	Lecanemab	Incremental vs. SoC
Community	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]

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

A.2.3 Multistate survival model

The multistate survival model used to estimate time-varying transition probabilities from Clarity AD data has been re-run for the indicated population. The methodology for deriving transition probabilities is the same as for the ITT population described in detail in the clarification questions response 8.d).

In the base case, the multistate survival model uses data from the Clarity AD core study period (0-18 months), discussed in section A.2.3.1. Three scenarios are explored using data from the OLE phase of Clarity AD (0-36 months), described in section 0.

A.2.3.1 Clarity AD core study

The log-cumulative hazards by transition and treatment arm for the core study period of Clarity AD are presented in Figure 22. In the text and figures below, transition 1 refers to the transition from MCI due to AD to mild AD, transition 2 refers to mild AD to moderate AD, transition 3 refers to mild AD to MCI due to AD, and transition 4 refers to moderate AD to mild AD.

Treatment arm log-cumulative hazards are generally parallel for each transition; therefore, a joint (i.e., dependent) modelling approach was used, in which the treatment effect was represented by a covariate within the survival model for each transition and assumed to be constant on the associated scale. The smoothed hazard plots for lecanemab and placebo are presented in Figure 23 for each transition. For transitions 1, 2 and 3, the hazard appears to increase over time for both lecanemab and placebo. For transition 4, the hazard is relatively constant for lecanemab and placebo and both have wide confidence intervals.

Figure 22: Log-cumulative hazards 0-18 months, by transition and treatment

Abbreviations: AD – Alzheimer's disease; BW – bi-weekly; LEC – lecanemab; MCI – mild cognitive impairment; PBO – placebo.

Figure 23: Smoothed hazards 0-18 months, by transition and study arm

Abbreviations: CI – confidence interval.
Graph 1: MCI due to AD to Mild AD transitions. Graph 2: Mild AD to Moderate AD transitions. Graph 3: Mild AD to MCI due to AD transitions. Graph 4: Moderate AD to Mild AD transitions.

Separate statistical models were estimated for each transition. Six distributions were considered (exponential, Weibull, generalised gamma, Gompertz, log-normal, and log-logistic). Plots of observed vs predicted transition probability are presented in Figure 24 - Figure 27 for transitions 1 to 4, respectively. Given a clock-forward

approach was used, observations are considered using time from the start of the study (i.e., at baseline) for each patient, as opposed to time since entry into each health state. Consequently, the numbers at risk increase over time for all transitions other than transition 1 (MCI due to AD to mild AD), and increase from zero for transition 4 (moderate AD to mild AD, Figure 27) given no patients started Clarity AD with moderate AD.

The estimated transition probabilities for lecanemab and SoC for each transition for the first 18 months and for the full model time horizon are presented in Figure 28 - Figure 35. Plots were compared to the smoothed hazard plot for each transition to assess which distributions appropriately reflect the underlying hazard and could therefore be considered for use in the economic model. These distributions were then assessed based on visual and statistical fit to determine the most appropriate choice for the base case. The Akaike (AIC) and Bayesian Information Criterions (BIC) scores outlining statistical fit are presented in Table 27**Error! Reference source not found.** for each transition.

For transition 1 (MCI to mild AD; Figure 28 - Figure 29), the generalised gamma, log-normal, and log-logistic distributions estimated decreasing transition probabilities within the first 18 months. Similarly for transition 3 (mild AD to MCI; Figure 32 - Figure 33), the log-normal, and log-logistic distributions estimated decreasing probabilities and the generalised gamma distribution estimated plateauing transition probabilities within the first 18 months. These were inconsistent with the smoothed hazard plots which suggested increasing hazards over the duration of Clarity AD core study (Figure 23), hence these distributions were deemed inappropriate. The exponential distribution was also ruled out based on having a constant hazard. Of the remaining distributions for transitions 1 and 3, the Gompertz distribution was ruled out as it estimated implausible transition probabilities beyond 18 months, reaching 100% after approximately 7 years (transition 1) and 10 years (transition 3). The Weibull distribution was therefore selected as it reflected an increasing hazard during the first 18 months, had an appropriate visual and statistical fit and yielded plausible transition probabilities beyond 18 months. Therefore, the Weibull distribution was considered the most appropriate for both transition 1 and transition 3.

For transition 2 (Figure 30 - Figure 31), the exponential and log-normal distributions were deemed to not reflect the underlying hazards over the first 18 months due to constant and plateauing hazards, respectively. Also, the Gompertz and generalised gamma distributions estimated implausible transition probabilities beyond 18 months, reaching 100% after approximately 6 years. Of the remaining distributions, Weibull had the best statistical fit to the data so was considered the only appropriate selection for transition 2.

For transition 4 (Figure 34 - Figure 35), the smoothed hazard plots indicated no clear change in hazard over time. On this basis, statistical fit and the small number of patients at risk for this transition, the exponential distribution was identified as the optimal distribution for transition 4.

Figure 24: Observed vs predicted transition probability (transition 1, 0-18 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment; PBO – placebo.

Figure 25: Observed vs predicted transition probability (transition 2, 0-18 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment; PBO – placebo.

Figure 26: Observed vs predicted transition probability (transition 3, 0-18 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment; PBO – placebo.

Figure 27: Observed vs predicted transition probability (transition 4, 0-18 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment; PBO – placebo.

Figure 28: Estimated transition probabilities for transition 1 over 1.5 years (0-18 months MSM)

Abbreviations: lec – lecanemab; MCI – mild cognitive impairment; SoC – standard of care.

Figure 29: Estimated transition probabilities for transition 1 over 30 years (0-18 months MSM)

Abbreviations: lec – lecanemab; MCI – mild cognitive impairment; SoC – standard of care.

Figure 30: Estimated transition probabilities for transition 2 over 1.5 years (0-18 months MSM)

Abbreviations: lec – lecanemab; SoC – standard of care.

Figure 31: Estimated transition probabilities for transition 2 over 30 years (0-18 months MSM)

Abbreviations: lec – lecanemab; SoC – standard of care.

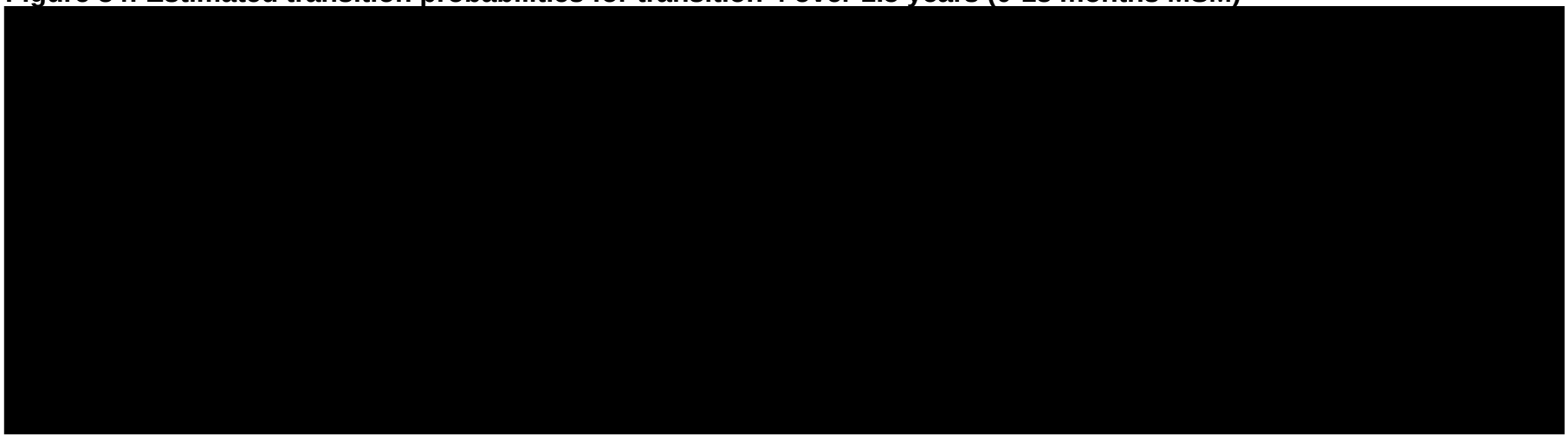
Figure 32: Estimated transition probabilities for transition 3 over 1.5 years (0-18 months MSM)

Abbreviations: lec – lecanemab; MCI – mild cognitive impairment; SoC – standard of care.

Figure 33: Estimated transition probabilities for transition 3 over 30 years (0-18 months MSM)

Abbreviations: lec – lecanemab; MCI – mild cognitive impairment; SoC – standard of care.

Figure 34: Estimated transition probabilities for transition 4 over 1.5 years (0-18 months MSM)



Abbreviations: lec – lecanemab; SoC – standard of care.

Figure 35: Estimated transition probabilities for transition 4 over 30 years (0-18 months MSM)

Abbreviations: lec – lecanemab; SoC – standard of care.

Table 27: AIC and BIC statistics for each transition, 0-18 months

Distribution	Transition 1 (MCI to mild AD)	Transition 2 (Mild AD to moderate AD)	Transition 3 (Mild AD to MCI)	Transition 4 (Moderate AD to mild AD)
AIC				
Exponential	2425.2	629.6	1135.4	**78.4**
Generalised gamma	2309.7	600.7	1100.2	80.6
Weibull	2329.4	**598.9**	1111.0	80.1
Gompertz	2356.5	600.8	1121.3	79.7
Log-logistic	2330.6	599.4	1108.8	81.1
Log-normal	**2307.9**	601.7	**1098.5**	80.6
BIC				
Exponential	2435.8	639.3	1145.1	**83.5**
Generalised gamma	2330.9	620.1	1119.6	90.8
Weibull	2345.3	**613.4**	1125.6	87.7
Gompertz	2372.4	615.3	1135.8	87.4
Log-logistic	2346.4	613.9	1123.3	88.7
Log-normal	**2323.8**	616.3	**1113.1**	88.2

Abbreviations: AD – Alzheimer's disease; AIC – Akaike information criterion; BIC – Bayesian information criterion; MCI – mild cognitive impairment.

A.2.3.2 Clarity AD OLE phase

To harness the longer follow-up available for lecanemab from the Clarity AD OLE in a scenario analysis, the multistate survival analysis was re-run using 36 months of data for lecanemab from the Clarity AD core and OLE phases (i.e. patients randomised to lecanemab in the core study who continued in the OLE phase). The multistate survival models were therefore fit independently, as the data were treated as a single arm, otherwise the same methodology was used as for the Clarity AD core study analysis (0-18 months).

In this scenario, transitions probabilities in the economic model are derived as follows:

- 0-18 months: lecanemab and placebo are taken from the Clarity AD core study (0-18 month) multistate model as described in Section A.2.3.1 for the base case analysis, to harness the benefits of the randomised, controlled core study period.
- 18-36 months: lecanemab transition probabilities are taken from the Clarity AD OLE multistate model. For SoC, transition probabilities are derived by applying the inverse treatment effect for lecanemab vs. placebo from the associated Clarity AD core study analysis (0-18 month) multistate model to the lecanemab transition probabilities, to preserve the relative treatment effect of the randomised, controlled core study period.
- Beyond month 36: SoC transitions are informed by natural history data with relative treatment effect applied through the time-to-worsening hazard ratios to inform lecanemab transitions, as per the base case.

The smoothed hazard plots by transition for the combined core and OLE periods (0-36 months) for lecanemab are presented are presented in Figure 36. For transitions 1 and 2, the hazard increases over time. For transitions 3 and 4, the hazard decreases over time, although transition 4 has wide confidence intervals.

Figure 36: Smoothed hazards 0-36 months, by transition and study arm

Abbreviations: CI – confidence interval.
Graph 1: MCI due to AD to Mild AD transitions. Graph 2: Mild AD to Moderate AD transitions. Graph 3: Mild AD to MCI due to AD transitions. Graph 4: Moderate AD to Mild AD transitions.

Plots of observed vs predicted transition probability are presented in Figure 37 - Figure 40. The estimated transition probabilities for lecanemab are presented in Figure 41 - Figure 44. Plots are shown for the 36-month follow-up period and over lifetime. The AIC and BIC diagnostic scores are presented in Table 28 for each transition.

Figure 37: Observed vs predicted transition probability (transition 1, 0-36 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment.

Figure 38: Observed vs predicted transition probability (transition 2, 0-36 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment.

Figure 39: Observed vs predicted transition probability (transition 3, 0-36 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment.

Figure 40: Observed vs predicted transition probability (transition 4, 0-36 months)

Abbreviations: AD – Alzheimer's disease; LEC – lecanemab; MCI – mild cognitive impairment.

Figure 41: Estimated transition probabilities for transition 1 over 1.5 and 30 years (0-36 months MSM)

Abbreviations: lec – lecanemab; MCI – mild cognitive impairment; SoC – standard of care.

Figure 42: Estimated transition probabilities for transition 2 over 1.5 and 30 years (0-36 months MSM)

Abbreviations: lec – lecanemab; SoC – standard of care.

Figure 43: Estimated transition probabilities for transition 3 over 1.5 and 30 years (0-36 months MSM)

Abbreviations: lec – lecanemab; MCI – mild cognitive impairment; SoC – standard of care.

Figure 44: Estimated transition probabilities for transition 4 over 1.5 and 30 years (0-36 months MSM)

Abbreviations: lec – lecanemab; SoC – standard of care.

Table 28: AIC and BIC statistics for each transition, 0-36 months

Distribution	Transition 1 (MCI to mild AD)	Transition 2 (Mild AD to moderate AD)	Transition 3 (Mild AD to MCI)	Transition 4 (Moderate AD to mild AD)
AIC				
Exponential	1817.1	669.7	923.3	99.7
Generalised gamma	1779.1	612.8	**862.9**	100.0
Weibull	1793.3	619.4	918.9	98.0
Gompertz	1805.7	**612.7**	898.0	98.6
Log-logistic	1791.8	628.0	892.3	**98.0**
Log-normal	**1777.5**	635.8	885.8	98.0
BIC				
Exponential	1821.8	674.1	927.7	**102.3**
Generalised gamma	1793.1	626.1	**876.2**	107.9
Weibull	1802.7	628.3	927.7	103.2
Gompertz	1815.1	**621.6**	906.8	103.9
Log-logistic	1801.1	636.9	901.1	103.2
Log-normal	**1786.8**	644.7	894.7	103.2

Abbreviations: AD – Alzheimer's disease; AIC – Akaike information criterion; BIC – Bayesian information criterion; MCI – mild cognitive impairment.

For transition 1 (MCI to mild AD, Figure 41), the log-normal, log-logistic, and generalised gamma distributions were deemed inappropriate as they estimated decreasing probabilities of transition after approximately 1 year, which is inconsistent with the increase observed over time in the smoothed hazard plot (Figure 36). The exponential distribution was also ruled out based on the constant hazard assumption. Of the remaining two distributions, the long-term transition probabilities with the Gompertz distribution were implausible as these increased rapidly. The Weibull distribution also provided a better statistical fit than the Gompertz distribution.

For transition 2 (mild AD to moderate AD, Figure 42), the log-logistic and log-normal distributions were ruled out as these estimated transition probabilities which decreased over time after approximately 3 years. The exponential curve was also ruled out based on the constant hazard assumption. The generalised gamma,

Weibull and Gompertz distributions all estimated increasing transition probabilities over time, consistent with the smoothed hazard plot. However, the increase in transition probabilities estimated by the Gompertz and generalised gamma distributions were not clinically plausible, reaching 100% after approximately 8 years 5 years respectively. Therefore, the Weibull distribution was considered the only appropriate distribution for transition 2 based on the plausibility of the transition probabilities.

For transition 3 (mild AD to MCI, Figure 43), the generalised gamma, log-logistic and log-normal distributions were ruled out as they estimated transition probabilities that initially increased before decreasing. The exponential distribution was also ruled out based on the constant hazard assumption. The Gompertz and Weibull distributions were both considered appropriate based on having decreasing hazards over time, aligning with the smoothed hazard plot, and estimated comparable long-term transition probabilities. The Gompertz distribution provided the better statistical and visual fit.

For transition 4 (moderate AD to mild AD, Figure 44), all distributions except exponential estimated a decreasing hazard over time as observed in the smoothed hazard plot, although the small sample informing this transition should be noted, reflected in the wide confidence interval of the hazard plot (Figure 35). Only the Gompertz and exponential distributions were considered appropriate based on visual fit, with Gompertz providing the better visual fit of the two. Both provided similar statistical fit based on AIC and BIC scores.

Based on the above, the Weibull distribution was selected for transitions 1 and 2, aligning with the distributions used in the 0-18 months multistate model. Both Gompertz and Weibull were considered appropriate for transition 3, while both Gompertz and exponential were considered appropriate for transition 4. Therefore, three scenarios were explored applying different curve selections for months 18-36, summarised in **Error! Not a valid bookmark self-reference.Error! Reference source not found.**.

Table 29: Summary of 18-36 months multistate model scenarios

Scenario	Transition 1	Transition 2	Transition 3	Transition 4

1	Weibull	Weibull	Weibull	Exponential
2	Weibull	Weibull	Gompertz	Exponential
3	Weibull	Weibull	Gompertz	Gompertz

The first scenario explores the impact of aligning the distributions with the 0-18 months multistate model. The second and third scenarios explore the impact of varying distributions for transition 3 and 4. In the second scenario, the Gompertz curve is used instead of Weibull for transition 3 as it provided a better statistical fit. In the third scenario, the Gompertz distribution is used instead of exponential for transition 4 as it provided a better visual fit and similar statistical fit to the exponential distribution.

A.2.4 Mixed model for repeated measures

The multivariable mixed model for repeated measures (MMRM) used to estimate health state utility values from Clarity AD was re-run for the indicated population.

The methodology for the MMRM is in line with the MMRM for the ITT population, details of which are presented in the addendum to the CS submitted on 22nd April 2024, Section B.2.3.1.1. The statistical models tested in the backward elimination process for patient self-reported, patient-by-proxy, and caregiver self-reported responses are summarised in Table 30, Table 31 and Table 32, respectively.

Table 30: Summary of tested models - EQ-5D-3L UK, by patient self-reported

Covariates	Model Number				
	1	2	3	4	5
Baseline EQ-5D utility index score	X	X	X	X	X
Treatment group	X	X	X	X	
Use of AD symptomatic medication at baseline	X				
APOE4 carrier status	X	X	X		
Geographical region	X	X	X	X	X
Health state defined by CDR-SB at the time of observation	X	X	X	X	X
Presence of treatment-emergent IRR, ARIA-E, or ARIA-H (any grade) at the time of observation	X	X			

Abbreviations: AD – Alzheimer's Disease; *APOE4* – Apolipoprotein E4; CDR-SB – sum of boxes of the clinical dementia rating scale; IRR – infusion-related reactions; ARIA-E – amyloid related imaging abnormalities-edema and effusion; ARIA-H – amyloid related imaging abnormalities-haemosiderin

Table 31: Summary of tested models - EQ-5D-3L UK, patient-by-proxy

Covariates	Model Number			
	1	2	3	4
Baseline EQ-5D utility index score	X	X	X	X
Treatment group	X	X	X	X
Use of AD symptomatic medication at baseline	X	X		
APOE4 carrier status	X	X	X	
Geographical region	X	X	X	X
Health state defined by CDR-SB at the time of observation	X	X	X	X
Presence of treatment-emergent IRR, ARIA-E, or ARIA-H (any grade) at the time of observation	X			

Abbreviations: AD – Alzheimer's Disease; *APOE4* – Apolipoprotein E4; CDR-SB – sum of boxes of the clinical dementia rating scale; IRR – infusion-related reactions; ARIA-E – amyloid related imaging abnormalities-edema and effusion; ARIA-H – amyloid related imaging abnormalities-haemosiderin
Note: the terms Caregiver and Study Partner are used interchangeably.

Table 32: Summary of tested models – EQ-5D-3L UK, by caregiver

Covariates	Model Number				
	1	2	3	4	5

Baseline EQ-5D utility index score	X	X	X	X	X
Treatment group	X				
Use of AD symptomatic medication at baseline	X	X	X		
APOE4 carrier status	X	X	X	X	
Geographical region	X	X	X	X	X
Health state defined by CDR-SB at the time of observation	X	X	X	X	X
Presence of treatment-emergent IRR, ARIA-E, or ARIA-H (any grade) at the time of observation	X	X	X		

Abbreviations: AD – Alzheimer's Disease; *APOE4* – Apolipoprotein E4; CDR-SB – sum of boxes of the clinical dementia rating scale; IRR – infusion-related reactions; ARIA-E – amyloid related imaging abnormalities-edema and effusion; ARIA-H – amyloid related imaging abnormalities-haemosiderin
Note: the terms Caregiver and Study Partner are used interchangeably.

A.2.4.1.1 Patient-reported EQ-5D

A total of [redacted] EQ-5D patient-reported observations from [redacted] *APOE4* heterozygotes or non-carriers in the Intent To Treat Full Analysis Set (ITT FAS+) were available from the Clarity AD core study for the MMRM analysis. Only the patients with assessments available at baseline and at least one post-baseline visit (excluding those in the "severe AD" health state defined by CDR-SB, and those not assigned to a health state due to missing CDR-SB data) were considered for the analysis. Missing data were handled by MMRM as described in the Company Addendum section B.2.3.1.1.

Coefficients and statistical significance of each variable for the patient self-reported model are provided in Table 33. 'Use of AD symptomatic medication at baseline' (p=[redacted]) was eliminated from Model 1, 'presence of treatment emergent IRR, ARIA-E, or ARIA-H at the time of observation' (p=[redacted]) was eliminated from Model 2, '*APOE4* carrier status' (p=[redacted]) was eliminated from Model 3, and 'LEC10-BW' (p=[redacted]) was eliminated from Model 4, as they did not meet the p<0.1 threshold.

Table 33: Coefficients from tested models – EQ-5D-3L UK, patient self-reported

Covariates	**Model Number**				
	1	**2**	**3**	**4**	**5**
Baseline EQ-5D utility index score†	[redacted]***	[redacted]***	[redacted]***	[redacted]***	[redacted]***
LEC10-BW (vs placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
Use of AD symptomatic medication at baseline – No (vs yes)	[redacted]				
APOE4 carrier (vs non-carrier)	[redacted]	[redacted]	[redacted]		

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Geographical region – Asia-Pacific (vs North America)	[redacted]*	[redacted]*	[redacted]*	[redacted]*	[redacted]*
Geographical region – Europe (vs North America)	[redacted]*	[redacted]*	[redacted]*	[redacted]*	[redacted]*
Health state defined by CDR-SB at the time of observation – MCI due to AD (vs moderate AD)	[redacted]***	[redacted]***	[redacted]***	[redacted]**	[redacted]***
Health state defined by CDR-SB at the time of observation – mild AD (vs moderate AD)	[redacted]***	[redacted]***	[redacted]***	[redacted]***	[redacted]***
Presence of treatment-emergent IRR, ARIA-E, or ARIA-H (any grade) at the time of observation – Yes (vs no)	[redacted]	[redacted]			
Intercept	[redacted]***	[redacted]***	[redacted]***	[redacted]***	[redacted]***
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*p<0.1; **p<0.01; ***p<0.001

†Baseline EQ-5D utility index score represents the mean index score derived from patient self-reported EQ-5D for the ITT population. The coefficients estimated in each model are applied to the baseline EQ-5D index score to generate MMRM-derived utility scores.

Abbreviations: EQ-5D – EuroQol 5 dimensions; LEC10-BW – lecanemab 10mg biweekly dose; AD – Alzheimer's Disease; *APOE4* – Apolipoprotein E4; CDR-SB – sum of boxes of the clinical dementia rating scale; IRR – infusion-related reaction; ARIA-E – amyloid related imaging abnormalities-edema and effusion; ARIA-H – amyloid related imaging abnormalities-haemosiderin

In the final MMRM model for self-reported EQ-5D for patients (Model 5), baseline EQ-5D utility index score, geographical region, and health state defined by CDR-SB at the time of observation were included.

Notably, the mild AD health state was associated with a higher coefficient ([redacted] [moderate AD as reference], p=[redacted]) than MCI due to AD ([redacted] [moderate AD as reference], [redacted]). This is consistent with the result of the ITT FAS+ MMRM presented in the addendum to the CS, section B.2.3.1.2. A similar trend was observed in the meta-analysis by Landeiro et al. 2020 which illustrates that while patient-by-proxy EQ-5D utility scores decreased as patients progressed from MCI due to AD to mild AD, patient-reported EQ-5D utility scores remained relatively constant.[5]

Goodness-of-fit statistics for all models tested for patient self-reported EQ-5D values are provided in Table 34. Model 5, the most parsimonious model, provided the lowest AIC and BIC scores.

Table 34: Goodness of fit statistics – EQ-5D-3L, patient self-reported

Model	N	Log Likelihood	Df	AIC	BIC
M1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

M2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DF is calculated as the dimension of the model, which is based on # of parameters from mean structure (including intercept) and covariance structure (unstructured: 6)
Abbreviations: AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; df - degrees of freedom; M = model; N = number of individuals included.

At baseline, the mean index score derived from patient self-reported EQ-5D for the modified population was [redacted] (n=[redacted]). The coefficients estimated in Model 5 were applied to the baseline EQ-5D index score to generate MMRM-derived utility scores (Table 35).

Table 35: MMRM-derived health state utility scores, patient self-reported

Health state	**Lecanemab**	**Placebo**
MCI due to AD	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]
Moderate AD	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's Disease; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures.

A.2.4.1.2 Patient-by-proxy EQ-5D

A total of [redacted] patient-by-proxy EQ-5D observations from [redacted] study partners of *APOE4* heterozygous carriers or non-carriers from the ITT FAS+ dataset were available from the Clarity AD core study dataset for the MMRM analysis. Only the individuals with assessments available at baseline and at least one post-baseline visit (excluding those in "severe AD" health states defined by CDR-SB, and those not assigned to a health state due to missing CDR-SB data) were considered for the analysis. Missing data were handled by MMRM as described in the Company Addendum section B.2.3.1.1.

Coefficients and statistical significance are provided in Table 36 for the models tested for patient-by-proxy EQ-5D. 'Presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation' (p=[redacted]) was eliminated from Model 1, 'Use of AD symptomatic medication at baseline' (p=[redacted]) was eliminated from Model 2, and '*APOE4* carrier status' (p=[redacted]) was eliminated from Model 3, as they did not meet the p<0.1 threshold. In the final MMRM model for patient-by-proxy EQ-5D (Model 4), baseline EQ-5D utility index score, treatment group, geographical region, and health state defined by CDR-SB were included.

Table 36: Statistical outputs from tested models – EQ-5D-3L UK, patient-by-proxy

Variable	Model Number			
	1	2	3	4
Baseline EQ-5D utility index score†	[redacted]***	[redacted]***	[redacted]***	[redacted]***
LEC10-BW (vs placebo)	[redacted]*	[redacted]*	[redacted]*	[redacted]*
Use of AD symptomatic medication at baseline – No (vs yes)	[redacted]	[redacted]		
APOE4 carrier status (vs non-carrier)	[redacted]	[redacted]	[redacted]	
Geographical region – Asia-Pacific (vs North America)	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region – Europe (vs North America)	[redacted]*	[redacted]*	[redacted]*	[redacted]*
Health state defined by CDR-SB at the time of observation – MCI due to AD (vs moderate AD)	[redacted]***	[redacted]***	[redacted]***	[redacted]***
Health state defined by CDR-SB at the time of observation – mild AD (vs moderate AD)	[redacted]***	[redacted]***	[redacted]***	[redacted]***
Presence of treatment-emergent IRR, ARIA-E, or ARIA-H (any grade) at the time of observation – Yes (vs no)	[redacted]			
Intercept	[redacted]***	[redacted]***	[redacted]***	[redacted]***
N	[redacted]	[redacted]	[redacted]	[redacted]

*p<0.1; **p<0.01; ***p<0.001
†Baseline EQ-5D utility index score represents the mean index score derived from patient self-reported EQ-5D for the ITT population. The coefficients estimated in each model are applied to the baseline EQ-5D index score to generate MMRM-derived utility scores.
Abbreviations: LEC10-BW – lecanemab 10mg biweekly dose; AD – Alzheimer's Disease; *APOE4* – Apolipoprotein E4; CDR-SB – sum of boxes of the clinical dementia rating scale; IRR – infusion-related reaction; ARIA-E – amyloid related imaging abnormalities-edema and effusion; ARIA-H – amyloid related imaging abnormalities-haemosiderin

Results indicated treatment with lecanemab was associated with a statistically significant increase in EQ-5D utility score. Unlike the patient self-reported results, less severe health states were associated with higher EQ-5D utility scores, as would be expected, with the coefficients decreasing with increasing AD severity (MCI due to AD: [redacted]; mild AD: [redacted] [moderate AD as reference], all p[redacted]).

Model goodness-of-fit statistics for all models tested for patient-by-proxy EQ-5D are provided Table 37. Model 4, the most parsimonious model, provided the lowest combined AIC and BIC score.

Table 37: Goodness of fit statistics – EQ-5D-3L UK, patient-by-proxy

Model	N	Log Likelihood	Df	AIC	BIC
M1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DF is calculated as the dimension of the model, which is based on # of parameters from mean structure (including intercept) and covariance structure (unstructured: 6)
Abbreviations: AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; df - degrees of freedom; M = model; N = number of individuals included

At baseline, the mean index score derived from patient-by-proxy EQ-5D for the modified population was [redacted] (n=[redacted]). The coefficients estimated in Model 4 were applied to the baseline EQ-5D index score to generate MMRM-derived utility scores (Table 38).

Table 38: MMRM-derived health state utility scores, patient-by-proxy

Health state	Lecanemab	Placebo
MCI due to AD	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]
Moderate AD	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's Disease; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures.

A.2.4.1.3 Caregiver EQ-5D

A total of [redacted] caregiver self-reported EQ-5D observations from [redacted] study partners of *APOE4* heterozygous carriers or non-carriers from the ITT FAS+ dataset were available from the Clarity AD core study for the MMRM analysis. Only the individuals with assessments available at baseline and at least one post-baseline visit (excluding those in the "severe AD" health state defined by CDR-SB, and those not assigned to a health state due to missing CDR-SB data) were considered for the analysis.

Coefficients and statistical significance are provided in Table 39 for the models tested for caregiver reported EQ-5D. 'LEC10-BW' (p=[redacted]) was eliminated from Model 1, 'presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation' (p=[redacted]) was eliminated from Model 2, 'Use of AD symptomatic medication at baseline' (p=[redacted]) was eliminated from Model 3, and '*APOE4* carrier status' was eliminated from Model 4 (p=[redacted]) as they did not meet the p<0.1 threshold.

Notably, 'presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation', 'Use of AD symptomatic medication at baseline' and '*APOE4* carrier status' was observed to have no statistically significant effect on EQ-5D scores reported by caregivers, patient self-reported or patient-by-proxy.

Table 39: Statistical outputs from tested models – EQ-5D-3L UK, by caregiver

Variable	Model Number				
	1	2	3	4	5
Baseline EQ-5D utility index score†	[redacted]***	[redacted]***	[redacted]***	[redacted]***	[redacted]***
LEC10-BW (vs placebo)	[redacted]				
Use of AD symptomatic medication at baseline - No (vs yes)	[redacted]	[redacted]	[redacted]		
APOE4 carrier (vs non-carrier)	[redacted]	[redacted]	[redacted]	[redacted]	
Geographical region – Asia-Pacific (vs North America)	[redacted]**	[redacted]**	[redacted]**	[redacted]**	[redacted]**
Geographical region – Europe (vs North America)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state defined by CDR-SB at the time of observation – MCI due to AD (vs moderate AD)	[redacted]**	[redacted]**	[redacted]**	[redacted]**	[redacted]*
Health state defined by CDR-SB at the time of observation – mild AD (vs moderate AD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence of treatment-emergent IRR, ARIA-E, or ARIA-H (any grade) at the time of observation – Yes (vs no)	[redacted]	[redacted]			
Intercept	[redacted]***	[redacted]***	[redacted]***	[redacted]***	[redacted]***
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*p<0.1; **p<0.01; ***p<0.001

†Baseline EQ-5D utility index score represents the mean index score derived from patient self-reported EQ-5D for the ITT population. The coefficients estimated in each model are applied to the baseline EQ-5D index score to generate MMRM-derived utility scores.

Abbreviations: LEC10-BW – lecanemab 10mg biweekly dose; AD – Alzheimer's Disease; *APOE4* – Apolipoprotein E4; CDR-SB – sum of boxes of the clinical dementia rating scale; IRR – infusion-related reaction; ARIA-E – amyloid-related imaging abnormalities-edema and effusion; ARIA-H – amyloid-related imaging abnormalities-haemosiderin

In Model 5, baseline EQ-5D utility index score, geographical region, and patient health state defined by CDR-SB were included. Less severe health states defined by patient CDR-SB also associated with higher EQ-5D utility scores for caregivers, with the coefficients decreasing across AD severity levels (MCI due to AD: [redacted], p=[redacted]; mild AD: [redacted], p=[redacted] [moderate AD as reference]).

Model goodness-of-fit statistics for all models tested for caregiver EQ-5D are provided in Table 40. Model 5, the most parsimonious model, provided the lowest combined AIC and BIC score.

Table 40: Goodness of fit statistics – EQ-5D-3L UK, by caregiver

Model	N	Log Likelihood	Df	AIC	BIC
M1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DF is calculated as the dimension of the model, which is based on # of parameters from mean structure (including intercept) and covariance structure (unstructured: 6)

At baseline, the mean index score derived from caregiver self-reported EQ-5D was [redacted] (n=[redacted]). The coefficients estimated in Model 5 were applied to the baseline EQ-5D index score to generate MMRM-derived utility scores (Table 41).

Table 41: MMRM-derived health state utility scores, caregiver

Health state	Lecanemab	Placebo
MCI due to AD	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]
Moderate AD	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's Disease; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures.

A.2.4.1.4 MMRM-derived health state utilities

Consistent with the MMRM results and base case presented in the addendum to the CS, patient-by-proxy utilities were preferred in the base case due to the counterintuitive results observed for the patient-reported MMRM (i.e. more severe health states having higher utilities). The final list of health state utilities used in the economic analysis is presented in section A.2.5, Table 42.

A.2.5 Health state utility values

As described in the draft guidance response, section 3.16, the health state utilities used in the economic analysis along with their sources and the rationale for each, are presented in Table 42.

Table 42: Source and justification for health state utility values used in the economic analysis

Health state	Utility value		Source	Proxy or self-reported utilities	Justification and reference in submission
	Lecanemab	Placebo			
Patient – community					
MCI due to AD	[redacted]	[redacted]	Clarity AD, MMRM	Patient-by-proxy	• A mixed model for repeated measures (MMRM) was used to analyse EQ-5D data from Clarity AD, to align with the EAG-preferred base case (updated analysis for the indicated population presented in A.2.4; methods first described in CS addendum, section B.2.3 and section B.2.3.1.5) and in line with the recommendations of the NICE manual for health technology evaluations.[6] • Patient-by-proxy utilities were used to address counterintuitive patient-reported utilities (i.e. mild AD utility greater than MCI due to AD), supported by one clinician's feedback in the UK HTA advisory board (July 2023, Clarification response, B19)[7], and further clinical validation from two clinicians received in July 2024.[8] • Treatment-specific utilities were used in the base case, as the treatment group variable in the MMRM was statistically significant p<0.1).
Mild AD	[redacted]	[redacted]	Clarity AD, MMRM	Patient-by-proxy	
Moderate AD	[redacted]	[redacted]	Farina et al. 2020	Patient-by-proxy	• Utility decrements for the moderate and severe AD health states were obtained from published literature, in the absence of sufficient observations from Clarity AD (CS, document B, section B.3.4.4.1.1). • Farina et al. was selected as the most appropriate study from the SLR as it was the only exclusively UK study reporting EQ-5D-3L by-proxy utilities (CS, document B, section B.3.4.3.1).

Health state	Utility value		Source	Proxy or self-reported utilities	Justification and reference in submission
	Lecanemab	Placebo			
Severe AD	[redacted]	[redacted]	Farina et al. 2020	Patient-by-proxy	• Utility decrements from Farina et al. for moderate AD (-0.20) and severe AD (-0.30) were applied additively to the Clarity AD MMRM utility for mild AD (CS, document B, section B.3.4.3.1) to generate the community health states utilities. • Patient-by-proxy utilities were used for moderate and severe AD health states based on evidence presented by Landeiro et al., showing substantial divergence between patient-reported and patient-by-proxy reported EQ-5D from moderate AD onwards. This is supported by clinical expert feedback from the UK HTA advisory board (July 2023, CS, document B, section B.3.4.4.1) and further validation conducted in July 2024, stating that patient-by-proxy utilities provide more useful insights (than patient utilities) given the potential loss in accuracy of self-reported utilities seen with more significant cognitive decline.[8]
Patient – institution					
MCI due to AD	[redacted]	[redacted]	Farina et al. 2020	Self-reported	• Utility decrements from published literature were used in the absence of data from Clarity AD for institutional care setting and applied additively to the patient community health state utility values (CS, document B, section B.3.4.4.1.2) • As per the moderate and severe AD community health states, patient-by-proxy values were used for moderate AD and severe AD for the same reasons as community health states (CS, document B, section B.3.4.4.1).[8] • Farina et al. was selected as the most appropriate study from the SLR, for consistency with patient community utilities. • Utility decrements from Farina et al. of -0.01 were applied additively to the MCI due to AD and mild AD community health states, and -0.16 to moderate and severe AD community health states to derive the institution health state utilities.
Mild AD	[redacted]	[redacted]	Farina et al. 2020	Self-reported	
Moderate AD	[redacted]	[redacted]	Farina et al. 2020	Patient-by-proxy	
Severe AD	[redacted]	[redacted]	Farina et al. 2020	Patient-by-proxy	
Caregiver – community					

Health state	Utility value		Source	Proxy or self-reported utilities	Justification and reference in submission
	Lecanemab	Placebo			
MCI due to AD	[redacted]	[redacted]	Clarity AD, MMRM	Self-reported	• A MMRM was used to analyse EQ-5D data from Clarity AD, to align with the EAG-preferred base case. • Health state utilities for carers are not treatment-specific, as the treatment group variable in the MMRM was not statistically significant. • EQ-5D utilities were used to align with the NICE manual; however these may underestimate the true impact benefit of lecanemab to caregivers. Evidence suggests that EQ-5D may be a suboptimal measure of the QoL impact of caring for people with AD, due to its focus on physical health.[9] Conversely, ZBI appears to correlate more closely with AD severity.[9] ZBI is focused specifically on assessing caregiver burden, using interviews to evaluate the stresses experienced by caregivers of people with AD. Therefore, ZBI may be more reflective of carer QoL than EQ-5D, which focuses on physical health. this is reflected in Clarity AD QoL results, as greater decline in EQ-5D was seen for lecanemab patients than placebo (non-significant, section A.1.1.2.1), contrasting with the statistically significant difference for lecanemab vs. placebo at 18 months observed for caregiver ZBI results (section A.1.1.2.3).The ZBI results align with the statistically significant clinical improvement observed in Clarity AD across all primary and secondary endpoints. Hence, the true benefit to caregivers of lecanemab may be greater than that shown in this analysis.
Mild AD	[redacted]	[redacted]	Clarity AD, MMRM	Self-reported	
Moderate AD	[redacted]	[redacted]	Black et al. 2018	Self-reported	• Utility decrements from published literature were used in the absence of sufficient observations for caregivers from Clarity AD to inform the moderate and severe AD health state utilities (see CS, document B, section B.3.4.4.2.1 Community care).

Health state	Utility value		Source	Proxy or self-reported utilities	Justification and reference in submission
	Lecanemab	Placebo			
Severe AD	[redacted]	[redacted]	Black et al. 2018	Self-reported	• Farina et al. was the only exclusively UK study identified through the SLR reporting caregiver utilities. However, the associated severe AD caregiver utility lacked face validity as they exceeded general population norms (see CS, document B, section B.3.4.4.2.1 Community care). • Black et al. was therefore selected from the SLR, as it included UK patients and provides EQ-5D-3L decrements for the moderate (-0.033) and severe AD (-0.053) health states from the mild AD health state utility.
Caregiver – institution					
MCI due to AD	[redacted]	[redacted]	Farina et al. 2020	Self-reported	• A utility decrement (-0.09) reported in Farina et al. is applied additively to the caregiver community health state utilities to derive those for the institutional care setting, to reflect the impact on the caregiver of the patient entering an institution. • This decrement is supported by clinical expert opinion obtained in July 2024 that institutionalisation of a loved one can have a significant impact on caregivers of patients with AD, who face feelings of guilt, relief, sadness, or anxiety, a mixture of emotions that can have a serious impact on QoL. Carers may also experience a sense of isolation or loss of identity when their caregiving role diminishes.[8] • Farina et al. was selected for the same reason as institution health states for patients (see CS, document B, section B.3.4.4.2 and B.3.4.4.2.2).
Mild AD	[redacted]	[redacted]	Farina et al. 2020	Self-reported	
Moderate AD	[redacted]	[redacted]	Farina et al. 2020	Self-reported	
Severe AD	[redacted]	[redacted]	Farina et al. 2020	Self-reported	

AD – Alzheimer's Disease; EAG – External Assessment Group; EQ-5D-3L – EuroQol-5 Dimension-3 Level; HTA – Health Technology Assessment; MCI – Mild Cognitive Impairment; MMRM – Mixed-Model Repeated Measures; SLR – systematic literature review; UK – United Kingdom; ZBI – Zarit Burden Interview

A.2.5.1 Caregiver utilities

As discussed in the draft guidance response (comment 9), a comparison of caregiver health state utilities applied for the respective approaches are presented in Table 43 below. For the additive approach, utility values are applied as presented in the table. For the increment approach, increments are applied relative to the state with the lowest utility value (severe AD in institution). For the decrement approach, decrements are applied relative to the state with the highest utility value (MCI due to AD in community).

In addition to the increment approach used in the base case, a scenario is also presented in A.2.2.2.3 using a patient and caregiver additive approach as described in comment 9.

Table 43: Caregiver utilities: additive, increments and decrements

Health state	Additive approach	Increment approach*	Decrement approach*
Reference utility	[redacted]	[redacted]	[redacted]
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]

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment.
* increments/decrements are applied to each monthly cycle

A.2.6 Infusion cost hand search results

As detailed in the draft guidance response (comment 10), a hand search was conducted to review NICE TAs of monoclonal antibodies administered via IV infusion published over the last six years (2018-2024). The findings are presented in Table 44.

Table 44: IV administration costs

TA	Treatment	Indication	HRG code	Cost	Infusion time	Assumptions[10]
798	Durvalumab	Non-small cell lung cancer	SB12Z	£241	60 minutes	Simple chemotherapy, outpatient setting, nurse time 30 minutes, chair time 30-60 minutes
862	Trastuzumab deruxtecan	Breast cancer		£221	90 minutes	
540	Pembrolizumab	Hodgkin's Lymphoma		£236	30 minutes	
763	Daratumumab with bortezomib, thalidomide and dexamethasone	Multiple myeloma	SB14Z	£385	Infusion 1: 7 hours Infusion 2: 4 hours Subsequent infusions: 3 hours	Complex chemotherapy including prolonged infusion treatment, one hour of nurse time and over two hours chair time
897	Daratumumab with bortezomib and dexamethasone	Multiple myeloma	SB15Z	£471	Infusion 1: 7 hours Infusion 2: 4 hours Subsequent infusions: 3 hours	Subsequent elements of a chemotherapy cycle, outpatient setting. No timeframe defined.
585	Ocrelizumab	Multiple Sclerosis	AA30F	£532	Infusion 1: 2.5 hours Subsequent infusions: 3.5 hours	Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.

Abbreviations: EAG – External Assessment Group; IV – intravenous; N/A – not applicable; NHS – National Health Service; TA – Technology Assessment

A.2.7 APOE4 testing costs

The breakdown of APOE4 testing costs is presented in Table 45 and Table 46 below. In the absence of alternative costs, unit costs and assumptions are aligned with the NHSE BIA submission model, which did not detail the source of the costs. Unit costs for the test and one outpatient appointment are adjusted via a multiplier to reflect the cost of testing those who are APOE4 homozygous and therefore ineligible for treatment (15.3% of Clarity AD patients), thus not captured in the model cohort. In line with the assumptions in the NHSE BIA submission, genetic counselling is assumed to be offered to APOE4 homozygotes, of which half are assumed to take it up. The total cost of APOE4 testing used in the model is therefore [redacted].

Table 45: Costs of APOE4 testing and outpatient appointment corrected for testing of APOE4 homozygotes

Component	Unit cost	Source	Multiplier for proportion of patients that are APOE4 homozygotes	Source	Cost corrected for testing of APOE4 homozygotes	Total cost
Test	[redacted]	NHSE BIA submission Note, no source provided within the submission.	1.18 (=1/(1-0.153))	Table 6, Clarity AD CSR[11]	[redacted]	[redacted]
Outpatient appointment	[redacted]				[redacted]	

Abbreviations: AD – Alzheimer's disease; APOE4 – Apolipoprotein E4; ITT – intent-to-treat; MCI – mild cognitive impairment; NHSE – National Health Service England.

Table 46: Genetic counselling costs for APOE4 homozygotes

Component	Unit cost	Proportion of patients offered counselling	Proportion of those offered who take up counselling	Source	Total cost
Genetic counselling	[redacted]	15.3%	50%	Cost: As per NHSE BIA submission Proportion of patients offered counselling: As per NHSE BIA submission (APOE4 homozygotes). Proportion who take up counselling: As per NHSE BIA submission	[redacted]

Abbreviations: APOE4 – Apolipoprotein E4; MCI – mild cognitive impairment; NHSE – National Health Service England.

A.2.8 Micro-costing study

As detailed in the draft guidance response (comment 10), a micro-costing study of the healthcare professional time required for tasks related to administration of lecanemab was conducted to address the committee's request for a breakdown of resource use for the administration of lecanemab.

Details on how the Burcombe *et al.* paper was identified, the information extracted from the paper, the approach to costing for lecanemab, and validation of the micro-costing study are all presented in the draft guidance response (comment 10). Below, the results of both stages of clinical expert validation are presented.

Firstly, the company presented the information reported by Burcombe *et al.* to three HCPs (clinician [HCP1], nurse [HCP2], and pharmacist [HCP3]) who had UK clinical trial experience with lecanemab and asked them to update the tasks and HCP time accordingly to reflect expected lecanemab infusion in NHS practice. The mean active HCP time for each task was subsequently validated with another clinical expert (HCP4) who has UK clinical trial experience with lecanemab, for which the results of the first round (responses from HCPs 1-3, mean results) were presented. HCP4 was asked whether they agreed with the results, and if not, to provide their own estimate of active HCP time for each category.

The mean time for all tasks based on all four HCP responses was calculated as [redacted](Table 47 and Table 48). The corresponding costs were obtained from the PSSRU Unit Costs of Health and Social Care programme (2022-2027) (Table 49).[12] The total cost of drug preparation was estimated to be [redacted] (Table 51) and the total cost of all other administration tasks estimated to be [redacted] (Table 50).

In addition, the consumables required for IV infusion were informed by Burcombe *et al.*, inflated to 2023 values using the PSSRU inflation indices.[13] The initial mean cost of consumables from Burcombe *et al.* was [redacted], which, after adjustment for inflation, equates to [redacted]. Adding these to the total cost of drug preparation and administration yielded a total cost per lecanemab infusion of [redacted].

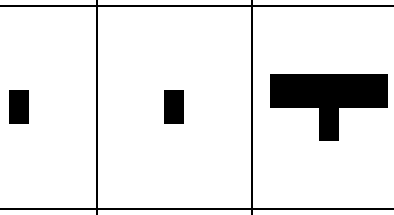
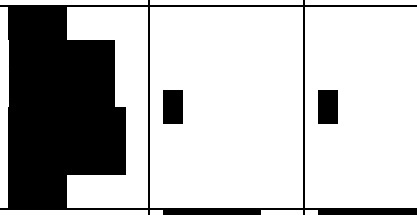
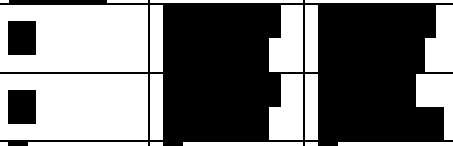
Table 47: Micro-costing HCP time and resource use

Task	Active HCP time (minutes)					PSSRU resource			
	HCP1	HCP2	HCP3*	HCP4	Average time	HCP1	HCP2	HCP3*	HCP4
Pre-infusion set up	[redacted]								
Drug preparation	As per Table 48								
Drug collection and check	[redacted]								
Pre-drug pt checks	[redacted]								
Drug administration	[redacted]								
Patient monitoring during administration	[redacted]								
Saline flush	[redacted]								
Remove and discard IV	[redacted]								

Patient monitoring post-administration	[redacted]								
Discharge patient	[redacted]								
Total (minutes)	[redacted]								

*As HCP3 is a pharmacist, they did not provide comments on the timing and resource use of these tasks
Abbreviations: HCP – healthcare professional; IV – intravenous; PSSRU – Personal Social Services Research Unit

Table 48: Drug preparation tasks

Drug preparation tasks (on ward)	Active HCP time (minutes)					PSSRU resource				
	HCP1	HCP2	HCP3*	HCP4	Average time	Assumptions	HCP1	HCP2	HCP3*	HCP4
Prepare worksheet (in pharmacy)										
Assembling product and consumables										
Checking of assembled product										
Preparation of the IV										
Final product check & release										
Total (minutes)										

*As HCP3 is a pharmacist and the only relevant task involved preparing a worksheet, their feedback was limited to this aspect
Abbreviations: HCP – healthcare professional; IV – intravenous; PSSRU – Personal Social Services Research Unit

Table 49: PSSRU cost inputs

PSSRU HCP	Cost per working hour (£)	Source
Healthcare Assistant (Band 3)	-	Not reported for Band 3
Healthcare Assistant (Band 4)	34	Band 4, hospital-based scientific and professional staff, PSSRU 2023 (page 88)
Nurse (Band 5)	47	Band 5 nurse, PSSRU 2023 (page 91)
Infusion suite nurse (Band 5)	47	Band 5 nurse, PSSRU 2023 (page 91)
Study nurse (Band 6)	57	Band 6 nurse, PSSRU 2023 (page 91)
Pharmacy Technician (Band 3)	-	Not reported for Band 3
Pharmacy Technician (Band 4)	34	Band 4, hospital-based scientific and professional staff, PSSRU 2023 (page 88)
Pharmacy Technician (Band 6)	50	Band 6, hospital-based scientific and professional staff, PSSRU 2023 (page 88)
Pharmacy Band 7	61	Band 7, hospital-based scientific and professional staff, PSSRU 2023 (page 88)
Pharmacy Band 8a	69	Band 8a, hospital-based scientific and professional staff, PSSRU 2023 (page 88)

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

Table 50: Cost of HCP time and resource use

Task	Cost (£)					Assumptions
	HCP1	HCP2	HCP 3	HCP4	Average cost	
Pre-infusion set up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Drug preparation	As per Table 51					
Drug collection and check	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-drug pt checks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Patient monitoring during administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Saline flush	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Remove and discard IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Patient monitoring post-administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Discharge patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Total cost (£)					[redacted]	-

Abbreviations: HCP – healthcare professional; IV – intravenous.

Table 51: Cost of drug preparation

Drug preparation tasks (on ward)	**Cost (£)**					
	HCP1	**HCP2**	**HCP3**	**HCP4**	**Average cost**	**Assumptions**
Prepare worksheet (in pharmacy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assembling product and consumables	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Checking of assembled product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preparation of the IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Final product check & release	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Total cost (£)					[redacted]	-

Abbreviations: HCP – healthcare professional; IV – intravenous.

A.2.9 Health state occupancy

As detailed in the draft guidance response, comment 6, health state occupancy graphs comparing outcomes from the cost-effectiveness model with Clarity AD are presented in Figure 45 and Figure 46 for lecanemab and SoC, respectively. In addition, health state occupancy graphs and tables for the scenario in which mortality data from Clarity AD are used directly for the first 18 months in the economic model are presented (Figure 47, Figure 48, Table 52, Table 53, and Table 54).

To compare model outcomes with the trial, the proportion of patients entering the model in the MCI due to AD and mild AD health states were aligned with the baseline distribution in Clarity AD as defined by CDR-SB (78.6% and 21.4%, respectively). Note, as the company has accepted the use of the EAG's preferred proportions (draft guidance response, comment 4), the model outcomes presented below are not reflective of the model base case.

Figure 45: Lecanemab health state occupancy, Clarity AD vs. CEM: base case

Abbreviations: AD – Alzheimer's disease.

Figure 46: SoC health state occupancy, Clarity AD vs. CEM: base case

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment; SoC – standard of care.

Figure 47: Lecanemab health state occupancy, Clarity AD vs. CEM: trial mortality

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

Figure 48: SoC health state occupancy, Clarity AD vs. CEM: trial mortality

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment; SoC – standard of care.

Table 52: Health state occupancy: Lecanemab, Clarity AD vs CEM

	MCI due to AD	Mild AD	Moderate AD	Severe AD	Death
Clarity AD					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					
CEM					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment, CEM, Cost-effectiveness model

Table 53: Health state occupancy: SoC, Clarity AD vs CEM

	MCI due to AD	Mild AD	Moderate AD	Severe AD	Death
Clarity AD					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					
CEM					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment, CEM, Cost-effectiveness model.

Table 54: Difference in health state occupancy Clarity AD vs CEM, lecanemab and SoC

	MCI due to AD	Mild AD	Moderate AD	Severe AD	Death
Lecanemab					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					
SoC					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					
Lecanemab vs. SoC					
13 weeks					
27 weeks					
39 weeks					
53 weeks					
65 weeks					
79 weeks					

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment, CEM, Cost-effectiveness model.

A.2.10 Mortality outcomes

As detailed in the draft guidance response, comment 6, a scenario was explored in which the mortality data from Clarity AD are used directly for the first 18 months in the economic model. The associated probability of death per cycle for each health state is presented in Table 55.

Table 55: Probability of death by health state, Clarity AD

Health state	Multiplier	Probability of death	Source
MCI due to AD	N/A	[redacted]	Clarity AD
Mild AD	N/A	[redacted]	
Moderate AD	1.551 (=3.77/2.43)	[redacted]	Clarity AD, Crowell et al. 2023[15]
Severe AD	2.263 (=8.53/3.77)	[redacted]	

Abbreviations: AD – Alzheimer's disease.

Additionally, mortality outcomes based on the latest cost-effectiveness model and Clarity AD are presented in Table 56, using a HR of 1.00 (CS addendum assumption) and a HR of 0.63 (Crowell *et al.* 2023) for MCI due to AD and using the Clarity AD mortality rate directly for the first 18 months for comparison.

Table 56: Mortality outcomes, Clarity AD vs. CEM, MCI due to AD equal to general population vs. HR reported by Crowell et al.

Source	Time (weeks)					
	13	27	39	53	65	79
Lecanemab						
Clarity AD	[redacted]					
Model (MCI due to AD HR=0.63)	[redacted]					
Model (MCI due to AD HR=1.00)	[redacted]					
Model (trial mortality rate)	[redacted]					
SoC						
Clarity AD	[redacted]					
Model (MCI due to AD HR=0.63)	[redacted]					
Model (MCI due to AD HR=1.00)	[redacted]					
Model (trial mortality rate)	[redacted]					

Abbreviations: AD – Alzheimer's disease; HR – hazard ratio; MCI – Mild cognitive impairment; SoC – standard of care.

A.3 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Draft guidance response – EAG query

October 2024

File name	Version	Contains confidential information	Date
[ID4043]_Lecanemab_DG_EAG query_15Oct2024_REDACTED_FINAL	1.0	N	15th October 2024

A.1 Model changes since ACM1

Prior to appraisal committee meeting 1 (ACM1), Lecanemab CEM and BIM v7.0 (19Apr24) was submitted along with an addendum to the company's submission (22Apr24).

Following the ACM1 on 9th May 2024 there have been two version updates to the cost-effectiveness model (CEM) as described below.

A.1.1 CEM version 8.0

Key model changes from CEM v7.0 to CEM v8.0 were:

- [redacted] (see Response to EAG response to company addendum, dated 08May24)
- Added input cells for the MMRM utility analysis for patient, patient-by-proxy, caregiver
- Added NHSE model inputs for costs

The company had intended to submit CEM v8.0 soon after ACM1, however it was agreed with the NICE TA team during post-ACM1 discussion to provide the updated model as part of the draft guidance response instead.

A.1.2 CEM version 9.0

The only model change that affects the ICER from CEM v8.0 to CEM v9.0 in addition to the base case changes as detailed in the draft guidance response comment 1 was:

- Correction to an error in calculating lecanemab monitoring costs in engine to align with the way other costs were applied (i.e. unit cost multiplied by the proportion of patients in each health state at each cycle).
    - Corrected formula in Engine_Lec sheet, cell EX12, then applied to rest of the column

=IF($D12<1,$EX$3,IF($D12<2,EX4,IF($D12<3,$EX$5,$EX$6))**)*(SUM(AU12:BB12)**+CHOOSE('Cell links'!F26,EW1*SUM(BG12:BH12),0))

    - The previous formula applied the monitoring costs as unit costs, without taking into account the proportions of patients in each health state at each cycle.

The company would like to apologise for not explaining this in the draft guidance response.

A.2 Company base case

A.2.1 Updated model inputs

As detailed in the draft guidance response comment 2, the CEM inputs have been updated to reflect the indicated population. Refer to the draft guidance appendix Table 20 for full details.

A.2.2 Updated company base case

Using the ACM1 company base case as a starting point, a correction was made to the formula for 'lecanemab monitoring costs' in the engine sheets before any adjustments were made (Table 1, correction 1.0).

The first model adjustment was to update the model inputs to reflect the indicated population, as per the MHRA marketing authorisation (Table 1, adjustment 1.1). Further model adjustments were made using this indicated population model as a starting point (Table 1, adjustments 1.2 to 1.9).

Table 1 shows how individual adjustments impact the results plus the combined effect of all the adjustments simultaneously, resulting in the updated company base case.

Table 1: Updated base case cost-effectiveness results (PAS price), individual ICER impact

Change	Related DG comment	Description adjustment	Justification adjustment	Model implementation adjustment	Incr costs (£)	Incr QALYs	ICER (£)	Cross-reference
ACM company base case					[redacted]	[redacted]	[redacted]	-
1.0 – corrected lecanemab monitoring costs	N/A	Correction to the formula for 'Lecanemab monitoring costs' in engines.	To align with the way other costs were applied (i.e. unit cost multiplied by the proportion of patients in each health states at each cycle).	CEM v9.0 reflects the correction to the formula for 'Lecanemab monitoring costs' in the Engine sheets.	[redacted]	[redacted]	[redacted]	See A.1.2. CEM version 9.0
1.1 – indicated population	N/A	Model inputs were amended to reflect the indicated population (*APOE4* non-carriers and heterozygotes).	As per the MHRA marketing authorisation.	CEM v9.0 additionally reflects the updated model inputs for the indicated population	[redacted]	[redacted]	[redacted]	See DG response comment 2 and DG appendix, Table 20.
1.2 - Removal of serious AEs	N/A	Removal of serious AEs due to overlap in the classification of severity and seriousness in Clarity AD	To avoid double counting of serious AEs.	Serious AEs are removed from CEM v9.0.	[redacted]	[redacted]	[redacted]*	See DG response comment 2.
1.3 – EAG's preferred baseline proportions of MCI due to AD and mild AD	3.8	Baseline proportion of patients with MCI due to AD and mild AD aligned with EAG preference, and the weighted discontinuation rate applied†	To align with EAG's base case (assumption 1) and clinical feedback.	Clinical data sheet: C17, select Yes. Weighted discontinuation rates are reflected in CEM v9.0.	[redacted]	[redacted]	[redacted]*	See DG response comment 4

Change	Related DG comment	Description adjustment	Justification adjustment	Model implementation adjustment	Incr costs (£)	Incr QALYs	ICER (£)	Cross-reference
1.4 – Modelling approach	3.12-3.13	Modelling approach: multistate survival model	As per committee's preference, the multistate survival model appropriately handles competing risks, whilst also limiting to a maximum of two transitions from each health state.	Key results: C20, select multistate	[redacted]	[redacted]	[redacted]*	See DG response comment 6.
1.5 – Mortality HR	3.12-3.13	Mortality HR for MCI due to AD: 0.63 (Crowell et al.)	As per committee's request to use transition probabilities in the model that lead to outcomes and mortality benefit consistent with trial data and clinical expectations.	Clinical data sheet: C94, select Crowell et al, 2023	[redacted]	[redacted]	[redacted]*	See DG response comment 6.
1.6 – Caregiver QoL	3.16	Caregiver QoL modelled as utility increments	Modelling caregiver utilities as increments, rather than decrements, to circumvent the 'carer QALY trap', as this method does not penalise extended survival time	Key results sheet: C56, select utility increment, or Utility data sheet: C77, select utility increment	[redacted]	[redacted]	[redacted]*	See DG response comment 9.
1.7 – *APOE4* testing	N/A	Inclusion of *APOE4* testing for all patients tested (including *APOE4* homozygotes)	To align with EAG's base case (assumption 8).	Cost data sheet: C84, select Yes	[redacted]	[redacted]	[redacted]*	See DG response comment 2 and DG appendix A.2.7)

Change	Related DG comment	Description adjustment	Justification adjustment	Model implementation adjustment	Incr costs (£)	Incr QALYs	ICER (£)	Cross-reference
1.8 – Admin cost source	3.17	Lecanemab administration cost source: micro-costing study	As per committee's request, used a lecanemab administration cost based on a breakdown of resource use.	Cost data sheet: C34, select micro-costing	[redacted]	[redacted]	[redacted]*	See DG response comment 10 and DG appendix A.2.8).
1.9 – Revised PAS	3.24	Revised PAS	N/A	Key results sheet: update C56, C58	[redacted]	[redacted]	[redacted]*	See DG response comment 13.
Revised company base case				**ACM COMPANY BASE CASE + correction 1.0 + adjustments 1.1-1.9**	[redacted]	[redacted]	[redacted]	See DG response comment 1.

Abbreviations: DG – draft guidance; ICER – Incremental cost-effectiveness ratio; PAS – Patient Access Scheme; SoC – standard of care
*Individual ICER impact for changes 1.2 onwards are presented versus the indicated population ICER 1.1 (which includes correction 1.0)

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments **5pm** on **Friday 20 September 2024**. 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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Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

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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.
	Alzheimer's Research UK has received sponsorship for the Research Conference 2024 Eisai Europe Limited (Conference platform and keynote speaker sponsor - £4,200) in the last 12 months.
	
	Several projects under the Dementia Consortium umbrella, funded in early 2022, are either ongoing or have been recently terminated.
	
	The Dementia Consortium brings together experts in target biology from academia and drug discovery experts from industry. The project provides funding and in-kind support for research projects typically 2 to 3 years in duration. Alzheimer's Research UK and the Dementia Consortium Industry partners, which includes Eisai, share the cost and risk of early-stage dementia drug discovery.
	
	VAPB: ER-mitochondria signalling as a new target for Dementia (VAPB-PTPIP51 tethering)
	• Status: Ongoing
	• Funding: Eisai provided £148,272.07, invoice dated 10 March 2022
	
	C9ORF72: Identification of tool compounds targeting the SRSF1-dependent nuclear export of pathological C9ORF72-repeat transcripts
	• Status: Project terminated after funding partners decision meeting in May 2023
	• Funding:
	  ○ Eisai provided £28,588.86, invoice dated 1 October 2022
	  ○ Takeda provided £23,270.10, invoice dated 31 August 2022
	
	Kings/ALS: Validating new promising drug targets in Amyotrophic Lateral Sclerosis
	• Status: Ongoing, the whole project was paid upfront by all partners
	• Funding: Takeda provided £97,377.90, invoice dated 11 November 2022

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Name of commentator person completing form:	[redacted]

Comment number	**Comments**

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments **5pm** on **Friday 20 September 2024**. Please submit via NICE Docs.

	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	**Ongoing review of long-term data on lecanemab is needed**. The recent 36-month results from the Clarity AD trial show that lecanemab slowed disease progression in patients over three years, demonstrating the need for them to stay on the treatment long term. The study also found that a patient's Alzheimer's disease worsens after they stop treatment. According to Eisai, rates of adverse side effects associated with lecanemab, including brain bleeding and swelling, dropped after six months of treatment.[i] This could indicate a reduced need for intensive monitoring in the later phases of treatment, suggesting that a single cost estimate for the entire duration of treatment delivery and monitoring may not be appropriate, and should be adjusted over time. Despite limitations of the findings presented at the Alzheimer's Association International Conference in July 2024, including the absence of a placebo arm in the extension phase, we believe there is value in NICE factoring these data into their evaluation of lecanemab's long-term efficacy.
2	Further clarification is needed on the **assumptions NICE used when determining infusion costs**. Specifically, there is a notable discrepancy between the company's cost estimate of £207 and NHS England's figure of £565. This discrepancy suggests that NICE's cost assumptions, if aligned with NHS England's figure, may have significantly influenced the ICER. We obtained estimates from three clinicians regarding real-world infusion costs: 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 suggest that the actual real-world cost of infusion may be lower than the £565 figure currently used by NICE (approximately £300). While NHS England is the most appropriate stakeholder to provide such estimates, it would be valuable to understand the detailed rationale behind the significant difference between NHS England's figure and the company's and clinicians' estimates.
3	NICE, NHSE, and the company must **continue exploring the possibility of a managed access route** for lecanemab. We support NICE's suggestion for an updated managed access proposal to be submitted by the company, which would include more comprehensive data collection and plausibly cost-effective ICERs. We agree that the company's suggestion for NHS England to propose pilot sites for phased collection of real-world data could be a practical way forward. While we recognise that providing access to only a portion of the eligible population may not fully align with the principles of managed access or the Innovative Medicines Fund (IMF), it is important to consider the unique challenges that Alzheimer's disease presents and the innovative nature of lecanemab alongside the current lack of pathway for prescribing this treatment

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

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	and significant variation in diagnosis across the NHS. Allowing access to a targeted group of patients could still deliver: • meaningful insights for further research • help prepare the healthcare system for wider deployment of treatments in the pipeline • improve the lives of those affected by the disease. There is precedent for IMF treatments being delivered through selected centres: CSL Behring has worked closely with NHS England's chosen therapeutic centres to ensure that eligible patients could access treatment for severe haemophilia B as soon as possible.[ii] Concerns over the limitations of specialist resources, infrastructure, and equipment within the NHS for collecting Alzheimer's disease patient data 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.
4	We would like to understand **how the quality of life for carers was incorporated** into the evaluation process. Although this aspect is mentioned in the papers, it remains difficult to interpret, and we would appreciate receiving this information in non-technical language. Our supporters are keen to understand which aspects of carers' experiences were considered, how quality of life was measured and how this data influenced the decision-making. For example, the financial and productivity impacts on carers of Alzheimer's patients were not included in the model, which could be a significant oversight. The committee has noted that these costs fall outside the NICE reference case. Furthermore, we are interested in how informal care costs were considered in the evaluation. While lecanemab may not currently be deemed cost-effective due to other factors, nonetheless these considerations could have a substantial impact on the final ICER. A thorough assessment of the treatment's value should also consider that dementia costs are largely borne by individuals and families rather than the state. With approximately 700,000 informal carers in the UK providing 1.3 billion hours of unpaid care for dementia, translating to an estimated formal cost of £8.8 billion[iii]. Given these factors, we would like to understand **if there is potential to apply the non-reference case to more accurately reflect these significant costs**.
5	We would like to understand **how the MHRA label's recommendation to discontinue lecanemab treatment once a patient progresses to moderate Alzheimer's disease[iv] will impact the evaluation model**. This label indicates that treatment should be stopped at this stage, and we are interested in understanding whether and how this requirement will influence the model used for assessing lecanemab's cost-effectiveness. We would also like to understand how the restrictions in the MHRA's label, for example excluding people with two copies of the APOE4 gene, can be reflected in the economic model given this reflects a smaller potential patient population.
6	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

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	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, early treatments for Alzheimer's are 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.[v] [vi] 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

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- 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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Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments **5pm** on **Friday 20 September 2024**. Please submit via NICE Docs.

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[i] Eisai Biogen Alzheimer's drug Leqembi shows benefits over three years (cnbc.com)
[ii] PM HEMGENIX Managed Access UK (cslbehring.de)
[iii] Landeiro, F, Luengo-Fernandez, R, 2021 [in preparation], 'Economic burden of cancer, CHD, dementia, and stroke 2018'
[iv] MHRA Products | Product results
[v] Understanding medicines access: a look at the severity modifier and its impact (abpi.org.uk)
[vi] 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 the draft recommendation NICE has made whilst also recognising the disappointment that many

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	people may have experienced on learning the decision. We accept NICE's assessment that the drug does not meet their threshold for cost-effectiveness but include below new evidence and comments for NICE's consideration.
2	We acknowledge NICE's assessment of the lack of evidence on the long-term effects of lecanemab and the substantial uncertainties in the economic model, and recognise the challenges this creates in making an assessment on cost-effectiveness. We welcome NICE asking the company and NHS England to provide additional information to help address uncertainties, and look forward to seeing further information on this.
3	We would also encourage NICE to monitor and review real-world data on the benefits and risks of lecanemab being collected in countries where lecanemab is approved for use and from phase four clinical trials. This is particularly important given MHRA's decision to approve on safety and effectiveness grounds, but with some exclusions. There are opportunities to learn more about lecanemab on a real-world basis from the application of MHRA's decision.
4	It is positive that NICE have listened to the experiences of people with Alzheimer's disease, including individual patient experts and submissions from patient and carer organisations like ourselves. In particular, we welcome the recognition of the challenges the condition can bring for both the person with Alzheimer's disease and their carers, how Alzheimer's disease affects people differently, and the hope that a first potential disease-modifying treatment brings.
5	We welcome the recognition from NICE of the significant changes that would be required to the existing diagnosis and treatment pathway, which was a key point raised in our first submission. New research released since that submission has found that spending on diagnosis and treatment for dementia is equivalent to just 1.4% of dementia healthcare costs, whilst by contrast, unplanned hospital admissions make up almost a third of all dementia healthcare costs[1]. This demonstrates the lack of prioritisation of proactive and preventative care for dementia. Changes to the diagnostic pathway are urgently needed to increase access to the symptomatic treatments and interventions recommended by NICE. Further changes will be required to rollout the diagnostics needed to confirm eligibility for disease modifying treatments that may be approved in the future.
6	We welcome the recognition from NICE that inequalities may increase as existing services already under strain would be needed to deliver treatment. We also note a further important point from NICE about equality, that people with Down's syndrome, people with young-onset dementia and people from diverse backgrounds were not fully represented in the Clarity AD clinical trial, and that these groups are at risk of being excluded from accessing lecanemab. We urge NICE to continue to consider the impact of lecanemab on inequalities.
7	Alzheimer's Society has new evidence which has been published since the Society's submission to the NICE appraisal for lecanemab in November 2023. This is evidence commissioned from healthcare consultancy Carnall Farrar, on the scale, cost and impact of dementia, and evidence relevant to this appraisal will be presented in this submission.
8	Prevalence of Alzheimer's disease can be relevant to calculations of cost effectiveness of lecanemab due to increasing economies of scale. It is estimated that there are around one million people with dementia in the UK; and this is set to rise to 1.4 million by 2040[2]. It is estimated that 50% of people with dementia have mild dementia, 37% moderate dementia, and 13% severe dementia[3]. Estimates of the prevalence of Alzheimer's disease, from previous research, are that this accounts for between 50% and 75% of all cases of dementia[4] (sometimes co-existing with vascular dementia). This is consistent with the estimate used by NICE, that 6 in 10 people with dementia have Alzheimer's disease. The new evidence from Carnall Farrar did not produce estimates of the possible population eligible for DMTs for Alzheimer's disease but the estimates of future prevalence and disease severity may help with these calculations.

[1] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers
[2] Ibid
[3] Ibid
[4] https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/dementia_uk_update.pdf

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9	The current cost of dementia could be useful context to the appraisal of lecanemab. The total cost of dementia in the UK each year is £42billion; and this is set to rise to £90billion by 2040[5]. Unpaid care accounts for 50% of the total cost (£21.1bn), social care accounts for 40% (17.2bn), and healthcare accounts for 17% (£7.1bn)[6].
10	The draft guidance recognises that currently a third of people with dementia do not have a diagnosis. It also states that 'NHS England also noted that introducing disease-modifying treatments would substantially increase demand on primary care and memory clinics because of increased awareness of MCI and availability of treatment options'. Our first submission set out evidence for the benefits of diagnosis for individuals, including unlocking access to support, care and symptomatic treatments. Although creating capacity challenges for memory services in the short to medium term, more people with dementia getting a diagnosis would be a positive development. We would also like to share that new evidence has found that a cohort of people with undiagnosed dementia attend A&E, on average, 1.5 times per year; which is three times as much as people with similar characteristics without dementia (in a control group matched for age and comorbidity)[7]. This suggests a further value to diagnosis, in reducing the need for emergency care.
11	As the condition progresses, people with dementia spend longer in hospital for non-elective stays: on average, each year a person with severe dementia stays in hospital three times as long as someone with mild dementia (27.7 days vs 9.3 days)[8]. This could indicate potential benefits of reducing demand on hospital resources from lecanemab where it can delay progression through the stages of Alzheimer's disease.
12	As the condition progresses, the average cost of dementia per person rises significantly: from £29,000 per year for mild dementia, to £43,000 per year for moderate dementia, to £81,000 per year for severe dementia[9]. A key driver of the high costs for severe dementia is the need for social care. This could indicate potential cost savings from lecanemab where it can delay progression through the stages of Alzheimer's disease. There could also be benefits in reducing demand for social care. It is projected that by 2040, 76,000 more people with dementia will live in a residential home and 30,000 more in a nursing home[10]. It is also projected that by 2040, 61,000 more people with dementia are projected to be drawing on domiciliary care[11].
13	Carnall Farrar developed estimates of the potential cost savings of early diagnosis and treatment with acetylcholinesterase (AChE) inhibitors such as donepezil. Though these treatments aren't suitable for everyone with Alzheimer's disease, where they are effective, some research has found they have the potential to delay admission to residential care; though evidence is mixed, and more research is needed. Modelling suggests that the delay to admission to residential care could result in savings of up to £9,000 to £45,000 per eligible person[12]. These savings are distributed across the individual and their family and the state. It is possible that savings related to social care could be achieved by lecanemab if it is shown to delay admission to residential care.
14	NICE asked us to provide further information on an estimate of the proportion of social care costs paid for by individuals and their families. New modelling from Carnall Farrar (which was not published at the time of the first consultation) estimates that the cost of social care paid for by people with dementia and their families in the UK is £8.8 billion, which is 51% of the total cost of social care[13]. The percentage of social care costs that are self-funded or state-funded were based

[5] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers
[6] Ibid
[7] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-metrics-early-diagnosis-and-treatment
[8] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-metrics-early-diagnosis-and-treatment
[9] Ibid
[10] Ibid
[11] Ibid
[12] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-metrics-early-diagnosis-and-treatment
[13] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers

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	on ONS data for England, as limited data was available for the other devolved nations. The distribution will differ in Northern Ireland, Wales and Scotland. Overall, of the £42billion cost of dementia, it is estimated that 63% of these costs are shouldered by people with dementia and their families, with the majority due to the costs of unpaid care and the cost of social care[14].
15	NICE report that the impact on the finances and productivity of carers for people with Alzheimer's disease were not captured in their model. We would like to share some evidence on the impact of dementia on the finances and productivity of carers, for NICE's consideration. Over 147,000 working age carers supporting a person with dementia, have had to reduce their work commitments, or are having difficulty balancing work and caring[15]. A total of 112,540 are no longer in paid employment due to their caring responsibilities[16]. 39% of carers for people living with dementia are providing over 100 hours of care a week, and 60% are providing over 35 hours of care per week[17].
16	On mild cognitive impairment (MCI), the draft guidance notes that some people are followed up after an MCI diagnosis, but many are discharged back to primary care with the advice to be re-referred once symptoms progress. The draft guidance also notes that there are challenges with diagnosis of MCI and that people with MCI have no current treatment options. Alzheimer's Society believe there is a need for greater guidance on MCI and has called for this to be included in the NG97 guideline.

Insert extra rows as needed

Checklist for submitting comments

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- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

[14] Ibid

[15] https://www.alzheimers.org.uk/sites/default/files/2019-10/The%20economic%20cost%20of%20dementia%20to%20English%20businesses%20-%202019%20refresh%20-%20Final%20complete.pdf

[16] Ibid

[17] https://digital.nhs.uk/data-and-information/publications/statistical/personal-social-services-survey-of-adult-carers/england-2021-22

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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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Name of commentator person completing form:	[redacted]

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1	The decision appears to have hinged on the cost effectiveness and health economic modelling, but this is very heavily redacted, and is therefore difficult to comment on. We appreciate that some information is commercial in confidence, and cannot be shared with stakeholders, but this need for confidentiality needs to be balanced against the need to be transparent enough to allow stakeholders to meaningfully engage in consultation. Most importantly, we need to be able to understand what are the key drivers of the decision and what are the key uncertainties that need to be resolved. Specifically, it would be helpful to have - An ICER range to indicate how close to meeting the cost effectiveness threshold the technology was - the relative impact of assumptions about infrastructure, diagnostic and monitoring costs relative to drug costs on the ICER - the impact of variations in assumptions related to care burden and transitions between disease states on the ICER
2	Molecular diagnostics for Alzheimer's disease are already contained within NICE guidance (NG97),and should ideally be routinely available to support clinical diagnosis (although they are currently only available in about 5% of services). We would question whether the costs associated with molecular confirmation of Alzheimer's disease pathology (CSF and/or amyloid PET) should be factored into cost effectiveness.
3	We would like to understand more about why the severity modifier was not applicable to Alzheimer's disease despite it being the leading cause of death in England.
4	The costs associated with Alzheimer's disease include both the economic costs of unpaid family carers and the reduction in quality of life associated with being a carer. We are unclear to what extent these aspects were factored into health economic modelling, and would welcome some clarification on this.
5	There is no current NICE guidance on diagnosis and management of mild cognitive impairment. Whilst we recognise that this is outside the remit of the TA committee, we feel that future evaluations would benefit from clearer standards of (molecular) diagnosis and care for MCI.
6	We welcome the committee's invitation of an updated managed access proposal, and consider that an appropriately designed managed access scheme would substantially resolve many of the uncertainties around real-world benefits and longer term transitions between disease states. We consider that the NHS would be the ideal setting for such a study, and the only way to resolve some of the specific considerations around real-world use in the UK. We would be keen that longer term data are not acquired only in less representative settings such as private care and international health systems not directly applicable to the NHS.

Insert extra rows as needed

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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	We consider that all the relevant evidence has been taken into account that is presently available.
2	Summaries of clinical and cost effectiveness are reasonable interpretations of the evidence

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3	The recommendations are sound and of a suitable basis for NHS guidance. However, our members pointed out the following considerations: Reflecting deeply as a society around the impact of dementia which is our biggest killer. Does the severity of AD need to be considered better by the NICE model. The costs of the system needing to be developed around this new medication are onerous- but again we need to reflect the needs of the population as a health service. Managed access would need to be considered but should be carefully worked upon so as not to exclude those who find NHS care hard to access
4	Our members did not think that any aspect of the recommendations needed particular consideration to ensure unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation. However, Alzheimer's Disease risk is increased by poverty (access to hearing aids, smoking, diabetes, depression etc) limiting treatments on the NHS may arguably have an effect on marginalised communities. Clearly age is a non-modifiable risk component and women are more likely to develop AD due to their longevity. A complex pathway would clearly raise a barrier to care/treatment
5	We agree that more evidence is needed especially with regards to longer term outcomes and the impact of adverse events. However, such data will not be generated without interim access to this treatment to better understand the benefits it can provide and so managed access should carefully deliberated with consideration to ensure fair and equitable offer especially to such groups of society where the prevalence of AD is greatest.
6	

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):	Faculty of Public Health

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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	**Section 3.2 - Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease**

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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 **Friday 20 September 2024**. Please submit via NICE Docs.

	"Guidelines from the National Institute on Aging and the Alzheimer's Association define the MCI stage as mild changes in memory and thinking that are:" The National Institute on Aging recently withdrew their endorsement of these 'biological framework' criteria. Under this framework, amyloid positivity places a person on 'the Alzheimer's continuum' regardless of the presence or absence of symptoms. As a result, many are labelled as having Alzheimer's despite the fact that they do not have, and will not develop, dementia in their lifetime. NICE have have presumably chosen to change their approach from previous guidance and adopt this language in order to align with the language used in the lecanemab trial reports, in which a person with MCI (and therefore not dementia) is described as having 'early Alzheimer's disease'. However, it should be noted that these criteria are not universally accepted in the research field, and not how dementia (and Alzheimer's disease as a subtype) are understood in the community nor in most areas of medicine (particularly primary care, geriatric medicine and palliative care) outside of tertiary and research-based neurology and psychiatry (Smedinga, 2020, https://doi.org/10.1093/geront/gnaa113). Importantly, it should also be acknowledged that this characterisation does not fit the epidemiological neuropathological evidence particularly well. In the UK, analysis of the CFAS data found that only around 20% of dementia was attributable to Alzheimer's pathology (Matthews et al., https://doi.org/10.1371/journal.pmed.1000180), and similar analysis in the US with the Rush data estimated that around 1/3 of late life cognitive decline is attributable to Alzheimer's pathology (Boyle et al., https://doi.org/10.1093/brain/awab092). The 60% proportion of dementia attributable to Alzheimer's used in the draft guidance is not referenced, but comes from clinical studies which are subject to potential selection biases because of the nature of patients who present to the services where these clinical codes are generated. The disconnect between clinical experience and pathological data is one of the key concerns about the biological framework language that NICE have chosen to adopt here, without appropriate caveat. This is perhaps indicative of a lack of epidemiological expertise present at the NICE committee meeting to present the knowledge derived from population-representative studies of dementia.
2	**Section 3.2 - Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease** **"all people with MCI caused by Alzheimer's disease eventually progress to having dementia."** This statement should be supported by a reference, and the population representativeness of the cohort used to derive this statement should be scrutinised and made public. We have checked the committee papers and there is no reference offered to support this statement there either. We have concerns about the validity of this statement.
3	**Section 3.6 - Clinically meaningful treatment effect** **"lecanemab is disease-modifying"**

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	This is made as a statement of fact. But whether or not lecanemab is disease modifying, and to what extent it is disease modifying (and for whom), remains theoretical and debated rather than empirically demonstrated (Daly et al., 2024, https://doi.org/10.1002/alz.14114). The (unreferenced) reporting of 24-month open-label extension data to support this statement in the draft guidance does not mention the lack of proper control group for these data. And the possible effects of attrition are not explored. Further, one of the clinical experts suggests in their testimony that the outcome slopes are clearly diverging during the trial period and this is why disease modification can be assumed. But we invite this expert to review the number of participants contributing to these analyses at each time point (reported under the figures) to see the differential attrition which may have driven this divergence in the figure in which it occurred, we also invite them to re-review all of the figures across the various outcomes reported in the supplementary materials where this was not the case and the slopes were instead parallel.
4	**Section 3.6 – Clinically meaningful treatment effect** **"They noted that it equated to a slowing in disease progression of between 4 and 6 months."** Negating the empirical evidence of clinical meaningfulness thresholds (which the trial effect sizes are not close to), but instead adopting the company's post-hoc framing of the results as 'time saving' again assumes an extrapolation of trial data beyond 18 months and beyond the trial cohorts, which again is conjecture rather than empirically supported.
5	**Section 3.6 – Clinically meaningful treatment effect** **"Clinical experts consulted by the EAG also identified that a difference in CDR-SB of 0.451 would be seen as a clinically meaningful change by people with Alzheimer's disease."** This statement is not supported by any empirical evidence. The empirical evidence that does exist, as raised in our original submission (and outlined further up in this section) demonstrates that a clinical expert would be unlikely to be able to differentiate between the average person's decline on the drug compared to the placebo at 18 months. Some empirical evidence is required to support this notion that a non-noticeable change could be meaningful (in contrast, see Liu et al., 2023, https://doi.org/10.1016/S2666-7568(23)00193-9).
6	**Section 3.6 – Clinically meaningful treatment effect** **"It showed evidence that, at 24 months, people who had started Clarity AD on lecanemab had a 16% slower decline in CDR-SB than people who switched from placebo to lecanemab after the trial at 18 months."** Differential rates of attrition between these groups should be explicitly taken into account when presenting these open label extension data, and the resulting conclusions caveated.
7	**Section 3.6 – Clinically meaningful treatment effect** **"The clinical experts noted that CDR-SB is commonly used as an outcome measure for moderate to severe Alzheimer's disease. But, they explained that it is**

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	not very sensitive in detecting changes in early Alzheimer's disease, particularly for people with MCI." The section could usefully draw upon any of the secondary outcome scales of cognitive and/or functional status reported in the trials (e.g. ADAS-Cog), which are more granular and confirm the small effect size which is well below the established empirical estimates of what is a clinically noticeable change in these scores (Liu et al., 2021, 10.1016/S2215-0366(21)00197-8).
8	**Section 3.6 – Clinically meaningful treatment effect** **"The patient and clinical experts agreed that a 6-month delay in disease progression was a clinically meaningful difference. They thought that a 4- or 5-month difference was also likely to be meaningful. The patient experts added that any slowing of disease worsening would be meaningful because it would mean more time socialising, driving and being independent. The committee concluded that lecanemab had a clinically significant treatment effect."** It is especially important that these statements are all caveated with the fact that they are not supported by empirical evidence, and are all conjecture based on extrapolating the trial evidence beyond what we have direct evidence to support.
9	**Section 3.8 – Trial generalisability** **"Submissions from the Faculty of Public Health questioned whether functional unblinding might be a concern because of very different rates of infusion reactions for lecanemab (26.4%) and placebo (7.4%). The submissions also noted that baseline characteristics and the way people were diagnosed in the trial were different to the UK. The company explained that trial investigators were blinded to the occurrence of adverse events."** This appears to show a lack of understanding about what functional unblinding is. Functional unblinding occurs when participants correctly guess their treatment arm status following the experience of adverse events (or in the case of asymptomatic ARIA, a change in their treatment/monitoring regimen as a result of detection of these adverse events). The (blinded) investigators were collecting outcome measures which include patient/carer-informed judgements about functioning and quality of life. So concerns of functional unblinding are not allayed by this explanation and we suggest they re-read the published literature (Wolters, 2024, https://doi.org/10.1002/alz.13690; Van Gool, 2023, https://doi.org/10.1093/brain/awad171) for a full examination of the potential of functional unblinding in the lecanemab phase III trial. In the committee papers, the company report only sensitivity analyses for ITT and attenuation for ARIA status, but not for the more common infusion-related reaction. This is not discussed in the draft guidance.
10	**Section 3.8 – Trial generalisability** **"It also added that the Clarity AD baseline characteristics were considered generalisable to the UK by the clinical experts it consulted."** The average age in the Clarity AD trial was 71. The average age for people developing dementia in the MRC CFAS II study (the most recent population-representative

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	community-based dementia prevalence estimate study in the UK) was around 83. Only 8% of those in a US-based community-based sample with early AD would have been eligible for the trials. There is absolutely no doubt that there a significant challenges to generalising findings from trial cohorts to real-world clinics with systematic differences increasing the likelihood of side effects and decreasing likely effect size in real-world clinics (Burke, 2023, https://doi.org/10.1212/WNL.0000000000207914 ; Walsh, 2024, https://doi.org/10.1002/alz.14108). This needs significantly more attention in the draft guidance and the clearly incorrect statement that trials cohorts are generalisable to UK clinics must be addressed.

Insert extra rows as needed

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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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- 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.
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	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):	Royal College of Psychiatrists

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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.	[Insert disclosure here]
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]

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Example 1	We are concerned that this recommendation may imply that ……..
1	**Has all of the relevant evidence been taken into account?**

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	We are interested to know whether the committee sees any merit in considering the factors below when modelling of the cost effectiveness of using lecanemab in the NHS? The queries centre on whether adjusting (narrowing) the start and stop criteria leads to any meaningful impact on the cost-effectiveness? And if there is any impact, whether the committee sees a role for an optimised / managed use of the treatment as a result? (i.e. an outcome that would mean the drug is used in a way that is more restricted than the marketing authorisation?). See response below to next question. Thank you.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** 1. Adjusting the stop criteria to limit the use of lecanemab to a maximum treatment of 18 months? The marketing authorisation indicates treatment should be stopped on conversion to moderate dementia. Aside from the real-world uncertainties related to how this would be consistently determined in clinical practice, when considering overall cost effectiveness, would this be meaningfully changed if the duration of treatment was limited to a maximum of 18-months? Acknowledging there are uncertainties of this approach on future prognosis, when considering cost effectiveness, does the absence of definitive long-term data that clearly informs the optimal treatment duration argue in favour of matching the duration of treatment in clinical practice to the duration of treatment used in the original phase III study (i.e. to overlap with where the evidence-base is currently best understood)? For example, based on the data from the Clarity-AD study, in the sub-group who had serial amyloid PET scans, the mean change from baseline at 18 months was −55.48 Centiloids (CL) in the lecanemab group and 3.64 CL in the placebo group (difference, −59.12 CL 95% CI, −62.64 to −55.60; P<0.001). After 18 months of treatment, the average amyloid level was 23 CL in the lecanemab treatment group, which is below the threshold for "amyloid positivity" of approximately 25-30 CL (This precise threshold is debated). So, from a cost effectiveness perspective, does the status of the current evidence justify continued treatment beyond 18 months? A presumption here could be that for individuals who have not experienced amyloid reduction by 18 months, is it cost effective to continue until moderate stage reached despite no (significant) biomarker change? And for those who reached "amyloid negativity" over 18 months, is there clear evidence that continued treatment is cost effective? This approach does not inherently require retesting amyloid status at 18 months and is broadly consistent with a biomarker responder modelling referenced in the stop criteria for donanemab by the FDA. (Note: We are aware various non-amyloid mechanisms have been hypothesised to

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	influence outcome of amyloid immunotherapies, and after stopping treatment at 18 months amyloid levels are likely to slowly increase, but this suggestion relates to whether or not this approach is viewed by the committee as being more cost-effective given current status of evidence?). 2. Adjusting the start criteria to limit the use of lecanemab to individuals with early AD (MCI or mild) who are ApoE-4 non-carriers have any merit? The NICE draft guidance concluded that "lecanemab had a clinically significant treatment effect" (section 3.6, page 11) and this clinical benefit appears to be most pronounced in individuals who are APOE4 non-carriers (e.g. section 3.9, page 14: non-carriers, 41% slowing of decline; heterozygote, 30% slowing of decline; and homozygote 22% faster decline using CDR-SB). This is echoed in the Forest plots from the Clarity-AD phase III study. More favourable outcomes in the non-carriers vs carriers were also seen in the secondary outcome measures of ADAS-Cog-14; ADCOMS, and ADCS-MCI-ADL. It is our understanding there was also a negative "dose-response" relationship between APOE4 status and the prevalence and severity of ARIA. E.g. the non-carriers had the more favourable profile of adverse ARIA events (APOE4 non-carriers for ARIA-E the percentage with symptomatic ARIA-E = 1.4% with overall prevalence = 5.4%; and ARIA-H prevalence =11.9%). Given individuals who are APOE4 non-carriers appear to have the most favourable benefit vs risk profile (benefit the most with the lowest risk), does the committee see any merit in modelling the cost effectiveness where treatment is limited to individuals who are APOE4 non-carriers? We are mindful however that this could risks discriminating against people who may benefit from the drug based on genotype, which would raise ethical concerns, and note benefits were seen in the APOE4 heterozygous group as per the marketing authorisation.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Looking ahead, we would anticipate the cost effectiveness would be more favourable if the subcutaneous formulation of lecanemab received marketing authorisation along with blood-based biomarkers for amyloid, possible decreased frequency of administration and potential for stopping treatment based on changes in amyloid status. As and when these changes occur, we would NICE be reappraising the cost effectiveness?
4	**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?** We are not aware of any such concerns (other than the comment about restricting treatment based on regarding APOE4 genotype).
5	Dear NICE committee. We would like to thank the committee for the opportunity to respond to the consultation

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	regarding the draft guidance on lecanemab, and for all your hard work in producing such guidance. In replying we are mindful this has been a complex judgement and that a number of the analyses (such as various subgroup analyses) underpinning these recommendations remain confidential. We are interested to know whether the committee sees any merit in considering the factors below when modelling of the cost effectiveness of using lecanemab in the NHS? The queries centre on whether adjusting (narrowing) the start and stop criteria leads to any meaningful impact on the cost-effectiveness? And if there is any impact, whether the committee sees a role for an optimised / managed use of the treatment as a result? (i.e. an outcome that would mean the drug is used in a way that is more restricted than the marketing authorisation?).
6	

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NHS England Response to NICE on Infusion Costs for Lecanemab

Summary

In response to the publication of the draft appraisal recommendations for lecanemab, NHS England has undertaken a further review of infusion pricing options. Should a positive adoption recommendation be made by NICE, these costs would be met by integrated care boards (ICBs) as the responsible commissioners for most elements of the Alzheimer's clinical pathway. We believe that an appropriate alternative method for estimating the costs is to use an approach consistent with the pricing assumed within the NICE appraisal process for monoclonal antibodies (MABs) administered in the management of a confirmed COVID infection. Using this method, and subject to a coding guidance and practice change, NHS England's pricing team estimate a resulting indicative unit price, including Market Forces Factor (MFF), of £432.

Background

NHS England notes that within the appraisal process for lecanemab, a significantly lower price for the administration of an intravenous infusion has been proposed by the manufacturer, compared to the cost estimated by the NHS. NICE has subsequently requested further information from NHS England to inform further committee deliberation on this element of the wider cost-effectiveness assessment.

The costs of infusion are an important and potentially material element of the lecanemab cost effectiveness calculation, but NHS England would encourage some caution in focusing on only one element of costing, since NHS pricing typically works by charging healthcare activity to the relevant NHS commissioner based on established average resource requirements. NHS pricing is not based on costing episodes of care for an individual patient nor producing granular pricing specific to every combination of procedure, patient age, complexity or medical condition.

All costings within NHS England's submission are consistent with this 'average cost' principle, in most cases using published tariff (pricing) information to cost each step in the pathway. We have not for example suggested that outpatient, MRI or lumbar puncture costs should be varied from standard tariff, even though it is possible that actual resource requirements might differ from (and even be higher than) average for the specific cohort of patients potentially eligible for lecanemab.

NHS England's response, effectively on behalf of ICBs - the responsible commissioners (funders) of lecanemab infusions if routinely introduced into NHS care - is set out below:

Basis of NHS England's original infusion costing submission for lecanemab

As a recap, NHS England's original costing estimate submitted to NICE for the administration of lecanemab by infusion was based – as per the approach throughout our modelling - on identifying the average cost most likely to be charged under current NHS coding and pricing guidance. This charge would be made by NHS infusion clinics to ICBs as the responsible commissioners of this element of the pathway.

- There is not currently a specific NHS price for the infusion of lecanemab in the treatment of Alzheimer's disease
- Instead, based on current coding guidance, NHS England believes that the most likely price to be charged to ICBs based on recording an infusion procedure, administered as a day-case (non-admitted) attendance, and where a patient has a recorded diagnosis of Alzheimer's disease is £585. In this scenario, under the 'grouping' process that is undertaken to derive price, it is the patient's diagnosis and day attendance which are the primary drivers of the predicted average resource requirements, rather than the procedure itself.
- NHS prices are derived based on a combination of the procedure undertaken and other factors, such as the medical condition for which the procedure is being undertaken, age, length of stay etc. NHS England's infusion administration cost estimates are based on an assumption that the appropriate OPCS code for the delivery of lecanemab is X292: *Continuous intravenous infusion of therapeutic substance NEC*. The Health Resource Group (HRG) grouper does not consider X292 to be resource significant, so it ignores it when grouping to an HRG. If there are no other OPCS procedure codes present for the patient's care episode, then the grouper will use the diagnosis - ICD10 - code to determine the HRG instead.
- NHS England has checked the latest HRG Code to Group file, and listed the relevant ICD10 codes which group to WD02Z in Appendix 1. NHSE believes the patient spell would be coded to one of these together with X292 for the procedure. WD02Z is listed on tab 14a of Annex A of the recently published 2024-25 update. The status of WD02Z remains unchanged i.e. it does not have a national published price and the currency is not mandated. However, this is how we would think most providers would code the activity if submitting the patient care episode to SUS.
- The average cost of an infusion (X292) for other conditions is £585.43. The cost for WD02Z from the latest available National Cost Collection (2021/22) is £660.10.
- ICD10 codes mapping to WD02Z are set out in Appendix 1.

Use of a chemotherapy tariff as a proxy for the cost of lecanemab infusion

NHS England does not agree that a chemotherapy tariff, as proposed by the manufacturer, is an appropriate proxy for the likely costs of administering lecanemab by infusion. Lecanemab requires more complex preparation prior to its administration and carries a higher risk of adverse infusion reaction which will impact on treatment monitoring and staffing requirements. The cohort of patients potentially eligible for lecanemab will be older, and may also have more complex needs, on average, than those receiving chemotherapy.

Please provide further detail about the source and derivation of the cost code

The information used to calculate the infusion cost for disease modifying treatment comes from the NHS Secondary Uses Service (SUS) system. SUS is the single, comprehensive repository for healthcare data in England. SUS enables a range of reporting and analyses to support the NHS in the delivery of healthcare services.

Secondary Uses Service (SUS) - NHS England Digital

Tariff prices have traditionally been based on the average cost of services reported by NHS providers in the mandatory reference costs collection, which is conducted annually. The reference costs from which the tariff is produced for any given financial year are three years in arrears. Therefore, an uplift is applied which reflects pay and price pressures in the NHS and includes an efficiency requirement.

Please give estimates of the resource use anticipated to be associated with the cost code e.g. x hours of nurse time etc

It is not currently possible to undertake a bespoke bottom-up costing exercise for lecanemab infusion as this treatment is not currently routinely available to cost in actual clinical practice in the NHS. Even though there is some limited lecanemab use under trial conditions (largely led by academic units), this is unlikely to be in an equivalent setting nor represent the actual costs relevant to routine clinical care, nor is activity being undertaken in sufficient numbers to provide a robust basis for costing. The creation of a new price specific to the infusion of lecanemab would also have implications for other NHS pricing structures and could not therefore be progressed in isolation. This might be considered further should a positive recommendation be made for routine adoption of this treatment in the NHS.

Proposed Alternative Pricing Approach (Parity with COVID MAB Infusion Pricing)

NHS England is content to offer an alternative pricing approach which would essentially piggyback, and be consistent with, the pricing assumed within the NICE appraisal process for monoclonal antibodies (MABs) administered in the management of a confirmed COVID infection. In this scenario it is the recording of the administration of a high-cost monoclonal antibody which would drive the price paid.

The benefit of this approach is that:

- Pricing in this area is already supported by bottom-up costing work previously undertaken by COVID Medicines Delivery Units (CMDUs) and based on actual clinical practice
- Costs reflect the specific resource implications (medicine preparation, treatment monitoring requirements etc.) of the infusion of a monoclonal antibody rather than using another type of drug as an arbitrary proxy
- An equivalent minor change to NHS coding guidance could be enacted for the 25/26 financial year. Infusion clinic providers would need to ensure that the administration of lecanemab was specifically captured within SUS to trigger the pricing option.

The infusion 'spells' are expected to group to the core HRG *WD02Z Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider.* This is diagnosis driven HRG,. If there is a significant procedure recorded or done, then it will likely mapped to elsewhere in the HRG classification structure.

Prices calculated using 2022/23 cost data and 2022/23 HES activities will generate a core HRG for WD02Z. Any drugs administered in relation OPCS 4 code(s) of *X891 or X892: Monoclonal antibodies Band 1 or 2* will generate unbundled HRGs for high-cost drugs (XD19Z or XD20Z).

Infusion of nMABs in the treatment of Mild Cognitive Impairment (MCI) or mild dementia caused by Alzheimer's Disease (AD) is a new service. Activity would be expected to be recorded as a planned day case by acute (hospital) providers who submit activity to SUS. However the price would also be applicable if activity was recorded as an outpatient procedure. The price would also be used by ICBs to agree contract values with community providers if / where activity does not flow through SUS.

NHS England's pricing team estimate a resulting indicative local unit price, including Market Forces Factor (MFF) of £432. This is calculated by uplifting the £362 21/22 price using the annual inflationary % as published in the NHS Payment Scheme – which is 3.6% for 22/23, 4.1% for 23/24 and 3.9% for 24/25 (this was 0.6% but has recently been increased to reflect the national pay negotiations), plus average MFF.

Please explain how this cost compares with delivery of other IV medicines – e.g. monoclonal antibodies in other neurological conditions, for COVID-19 and chemotherapy and if there are differences, the reasons for these

As set out above, the proposed revised approach, which reduces the NHS's cost estimate of administering lecanemab by infusion from £585 to £432, would be consistent with the costings proposed for the infusion of monoclonal antibodies in the treatment of COVID. This was supported by bottom-up costing work undertaken on the basis of actual NHS use of monoclonal antibodies administered by infusion, by a sub-set of COVID Medicine Delivery Units (CMDUs).

Please note this approach would require a minor update to the annual coding guidance provided to NHS providers, and for providers to specifically record the administration of lecanemab in SUS.

In the scenario where DMTs for Alzheimer's are recommended for use in the NHS (through routine commissioning or managed access), please comment on whether NHSE would conduct an exercise to review this cost code after a period of data collection and how long such an exercise would take'

NHS England routinely reviews the calculations underpinning NHS pricing, and we would want to ensure this consistent process would also be used in this case. This standard review process uses data three years in arrears, using actual 'reference' costs submitted by multiple providers. The price used for infusion spell will therefore be automatically reviewed in due course using the standard reference cost process once sufficient patient volumes are available to make a calculation on average costs reliable.

Appendix 1

ICD10 Codes Mapping to WD02Z

Code	Code Description
A810	Creutzfeldt-Jakob disease
F000	Dementia in Alzheimer disease with early onset
F001	Dementia in Alzheimer disease with late onset
F002	Dementia in Alzheimer disease, atypical or mixed type
F009	Dementia in Alzheimer disease, unspecified
F010	Vascular dementia of acute onset
F011	Multi-infarct dementia
F012	Subcortical vascular dementia
F013	Mixed cortical and subcortical vascular dementia
F018	Other vascular dementia
F019	Vascular dementia, unspecified
F020	Dementia in Pick disease
F021	Dementia in Creutzfeldt-Jakob disease
F022	Dementia in Huntington disease
F023	Dementia in Parkinson disease
F024	Dementia in human immunodeficiency virus [HIV] disease
F028	Dementia in other specified diseases classified elsewhere
F03X	Unspecified dementia
G300	Alzheimer disease with early onset
G301	Alzheimer disease with late onset
G308	Other Alzheimer disease
G309	Alzheimer disease, unspecified

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	Not provided
Other role	Not provided
Organisation	Gloucestershire ICB
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

We note that the committee has asked for considerable additional information from both the submitting company and NHS England. We are therefore uncertain as to whether all the relevant evidence has been presented and considered.

NICE appears to have thoroughly considered the evidence it has in its guidance and recommendation against prescribing lecanemab on the NHS (at the current time). Given this evidence includes clinical effectiveness data indicating the medication slows cognitive decline by only 4-6 months, we agree there is only evidence of a limited benefit for the person. Qualitative data from the patient/carer perspective has been included in the committee slides and focuses on the benefits of slowing cognitive decline for the individual, although there is an acknowledgement within the economic analysis that the cost of the lecanemab pathway does not offer good value for money when weighed against the modest benefits for individuals with Alzheimer's disease.

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

The summaries of clinical and cost-effectiveness appear to be reasonable interpretations of the available evidence this far. We have significant concerns about the high degree of uncertainties in both the clinical evidence and economic modelling and analysis.

While lecanemab does show a disease-modifying effect, there remains uncertainty about whether this translates into a clinically meaningful change for patients. The current evidence suggests that the drug may slow cognitive decline by only 4-6 months.

Additionally, the treatment pathway for lecanemab is resource-intensive, requiring substantial capacity from both primary and secondary care. The associated costs, combined with the extensive changes needed in the assessment, diagnostic, treatment and post diagnosis pathway, indicate that lecanemab may not represent

good value for money for the NHS. Therefore, while the summaries acknowledge the potential benefits of lecanemab, they also appropriately weigh the significant financial and logistical challenges against these modest gains considering the demanding and intensive monitoring required to detect signs of serious side effects such as, brain swelling or bleeding. Currently there is a lack of capacity and infrastructure in the NHS to ensure safe and equitable use of lecanemab. Significant investment in NHS services including infrastructure, staffing and training would be required to support safe and effective use.

We have considerable concerns about the safety and efficacy of lecanemab. Whilst the MHRA has granted a marketing authorisation in the UK, the CHMP considered that overall, the benefits of treatment are not large enough to outweigh the risks associated with lecanemab and have to date refused to grant a license for use in the European Union.

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.

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

The recommendations made by NICE regarding the Alzheimer's drug lecanemab appear to be suitable and appropriate as a basis for NHS guidance. Therefore, 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.

The drug's benefits, while present, seem too limited to justify the associated costs and the demands of the assessment, diagnostic, treatment and post diagnostic pathway. Current evidence indicates that lecanemab slows the progression of Alzheimer's disease by just 4-6 months, with insufficient data on long-term benefits.

Additionally, the treatment pathway is both lengthy and demanding. It requires individuals to undergo 2-weekly infusions for up to 18 months, accompanied by regular maintenance scans. This treatment schedule could significantly impact the quality of life for both the person and their carers, especially considering the relatively modest clinical benefit observed. These factors suggest that, while lecanemab offers some promise, its overall value may not be sufficient to warrant widespread adoption within the NHS at this time. In Gloucestershire we would look forward to this guidance being reviewed as more evidence becomes available on the efficacy and longer-term benefits of the medication.

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?

The recommendation that lecanemab be available only through private healthcare could exacerbate health inequalities, as individuals from lower socio-economic backgrounds will not be able to access the medication. This concern must be weighed against the reality that offering lecanemab on the NHS would require substantial increases in service delivery, potentially increasing existing inequalities within the healthcare system. Balancing these factors is crucial to ensuring equitable access to care without overburdening current NHS resources.
We would hope that further clinical trials for lecanemab would include groups that were underrepresented in the previous trials so that when a disease-modifying drug is approved for prescription by the NHS, it would be available for the whole population.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Not provided
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

I believe the crucial claim of a significantly different rate of slowing of cognitive decline in the van Dyck et al paper ($p < 0.001$, or one in a thousand) has not been widely recognised as so small that it is easily explained as a placebo effect.
The reason is that in the CDR test observers use structured interviews to rank 6 items as normal, questionable, mild, moderate, severe, awarding : 0, 0.5, 1, 2, and 3, respectively. Higher scores show greater decline. The 6 items are cognitive memory, orientation, judgment/ problem solving plus three domains of function (community affairs, home/hobbies, personal care). The scores for the six domains (range from 0 to 3) tested can be summed (CDR Sum of Boxes or CDR-SB).
The van Dyck result was that the mean of the active group declined by 1.21 units over the 18 months of the study, which means the group declined between a “mild” and a “moderate” amount. That was only 0.45 units less than the placebo mean, so the difference is very small indeed. Half of a unit is less than equal to a rating of questionable, so it has no clinical value, especially as it is merely a subjective evaluation of the patients by the observer.

Since the p value indicates there really was a difference, how was it caused? It is easily explained by the patients speaking more positively to the person scoring their responses due to believing they had taken the active, and that was due to experiencing unusual headaches and inflammation at the site of injection as well as the subtle attitude differences of other staff.

This result supports the notion that simply removing a (chemical) symptom of a stressed or faulty metabolism does not lead to a cure, compliant with the basic tenet in medicine that treating a symptom does not cure.

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

I believe they are

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

I believe they are

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?

Not to my knowledge

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	NHS Herefordshire and Worcestershire ICB
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

Uncertain

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

No. There is considerable uncertainty within the economic model. In addition, there has not been any assessment/recognition of the wider impact associated with the identification of patients who:
• Are ineligible for treatment including moderate to advanced disease
• Have other types of dementia
• Receive a non-dementia diagnosis
• Require psychological support post-diagnosis
• Require counselling following genetic testing

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

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Not provided
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

A big issue in dementia research is the gradual nature of the deterioration faced by patients. This proves real challenges for drug studies, which are generally limited in time due to their significant costs. This is a real challenge in providing the depth of clinical and financial outcome data for this group of patients, which will remain a challenge in assessing the cost effectiveness of treatments. Good quality evidence will only be established with clinical and pharmaceutical collaboration. The precedent of the risk sharing scheme model for Multiple sclerosis may well be relevant here.

The further unpublished outcome data from the extension studies are potentially important, but will be limited as these are not randomised studies. These have only been presented at meetings and not submitted to the peer review process then this is clearly problematic at present.

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

Given the approval situation it would be helpful if there was some modelling of the likely costs and outcome should patients be treated with these medications privately.

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

The issue with the current NICE guidance while accompanied with the MHRA approval is that these medications will not be offered by the NHS. However, patients and their families will still want these treatments. This is likely to lead to them being offered only by private health care. As the financial burden of dementia is soo severe for patients and families there is a risk of solidifying inequities and causing severe financial hardship to many. It is clear given the treatment cost, side effect profile and potential number of affected patients that this treatment could not have been broadly offered. However, It would seem likely that in younger onset patients in particular patients are likely to seek private treatment. If these treatments are significantly taken up privately this creates a significant risk to NHS services, as the selection of patients for treatment, monitoring of safety and also collection of outcome data will not be undertaken within NHS structures. However, it is likely any patients with symptomatic ARIA will present acutely to NHS services who may have limited information about the treatment. This situation will also not lead to the establishment of multi-disciplinary teams with expertise in managing these complications, that would likely improve clinical training and radiology training in recognising and managing ARIA. Therefore, in this situation NHS services may well be put at significant risk. With our stretched budgets there clearly is rationing of resources within the NHS. However, if there was a limited

approval for a subset of patients (? young onset dementia) this in my view would have been safer, as it would have helped progress the structures required to make biological diagnoses of Alzheimer's dementia within health boards and the establishment of the MDT structures required to safely select and monitor patients under treatment. Given that there will likely be further treatments evolving for these patients the lack of any NHS route to treatment risks the very poor current diagnostic infrastructure for dementias stagnating compared to other comparable nations. Some form of limited approval similar to the risk sharing scheme that was set up for relapsing remitting MS, targeted to a sub-group of patients would have been of benefit in evolving services and allowing for the collection of longer term clinical outcome and cost effectiveness data.

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?

In some ways the uniform nature of the lack of approval is not discriminatory. However, as dementia is the most expensive condition that a patient can have and given that the conditions are more common in patients of a lower sociodemographic status the current approval status risks further creating a two-tier structure of lack of access to treatment based on wealth. It also seems unfair, given our diagnostic services are so poor, that many patients are likely to pay considerable amounts of money for private assessments and investigations, but find they are not eligible for treatments thereafter anyway. Even in those that can pay for treatment, the private costs are likely to be high as will be their later care costs which may well cause hardship to their surviving relatives. Other health care models are more nuanced in their ability to share some of the costs within the health care structures, with patients paying the additional costs.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Alzheimer Scotland – Action on Dementia
Location	Not provided
Conflict	No
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. While we appreciate that NICE has a specific brief with regard to the NHS in England and Wales, it is an omission not to consider the potential impact of this treatment on overall social care costs alongside the impact that these treatments might have on individuals and families. We believe that this should be encouraged as part of the recommendation NICE made to the company and NHS England to further explore economic analysis and should be taken into account by the assessment committee. Whilst it is difficult to predict the full extent of the impact on social care and other aspects of health care, at a very basic level if these new treatments delay, prevent or avoid early admission to residential care or hospital for any reasonable period, then that could be a substantial cost saving. A one year delay or reduction in admission to residential care for example would equate to approximately £60-80,000 per person. We would argue that the fact that many people with dementia have to pay for this care, when in the later stages of the

illness their needs tend to be primarily health care needs places an unfair financial burden on individuals which new treatments could help alleviate.

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

No. Within the assessment process much has been made of what needs to change or be developed in order to bring this treatment into mainstream NHS as part of the costs benefit analysis. This is unfair and unreasonable. No new treatment should be measured against the NHS's lack of preparedness and loaded with these potential costs. It has been quite clear for many years now what the NHS needs to do in order to be ready for these new disease modifying treatments. This was set out as early as 2017 in the first Edinburgh Consensus paper, which explained in some detail of what needs to be put in place by the NHS and provided a consensual number of key recommendations that should have been implemented. The fact that there has been very little investment in ensuring our system is ready for these new drugs should not be part of the assessment process. It should be highlighted as a failing on the part of the NHS, and NICE should be recommending and reinforcing what is required by the NHS in order to deliver these treatments. This might be the first treatment of this nature to be assessed, but there will be others and the same problems will exist within our health system unless the NHS makes additional investment. If this continues to be part of the assessment process, then we believe that NICE is simply upholding the serious neglect and unfair treatment of people at risk or living with dementia.

In other areas of medicine such as cancer or MS treatments, there is an infrastructure that has been invested in over many years. Introducing new treatments to a well developed system is in our view far easier and far less expensive than where we are in terms of dementia care. If a new cancer treatment required the basic building blocks of our current system to be costed into an assessment, we doubt if that would be deemed cost effective. It is our opinion that the infrastructure changes and costs required within the NHS need to be assessed in a different way.

NICE should be considering whether or not it is reasonable to expect that the NHS has a duty to support people with dementia by investing in the development of new services such as brain health clinics and preparing new pathways using existing resources in order to be ready for the new evolution of treatments. We believe that it is a reasonable expectation, having worked with the Scottish Government and NHS Grampian to set up a Brain Health Clinic in Aberdeen to prepare for a new world of dementia prevention and treatment. We also know it is possible.
It is our view that the NHS has failed to plan and failed to prepare for the new treatments and that by placing the cost burden of this into this assessment, NICE are allowing the neglect and unequal treatment towards people at risk or living with dementia to be perpetuated.

We also do not think that framing the outcomes of the trials as a 4-6 month delay in the progression of the disease is meaningful. NICE has to consider that if at the end of the 18 month trial there is a clear clinical benefit of 27% less decline in cognitive function what this would mean for the potential increased impact that this could have on complementary non-pharmacological interventions.

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

No, they are clear but in our view they are wrong and at the very least NICE should issue guidance on what the NHS must do to prepare for future treatments if this nature as a minimum requirement.

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?

As is clear from our previous comments, we believe that there is an indirect discrimination of older people at risk or living with dementia through the NHS's lack of investment and lack of preparedness in developing new care pathways and diagnostic capacity for these new treatments. We believe that NICE should not be adding to this and should in fact be highlighting what new pathways the NHS require to develop and the cost of this should be part and parcel of the NHS spending plans and separated from the cost benefit assessment of this and other new treatments. If there is no clear commitment and guidance placed on the NHS to make the right level of investment in order to prepare for these new treatments, every future assessment will face the same challenge and this will more than likely mean that no new treatments of this nature will be approved. This would be wrong and leaves older people at risk or living with dementia with no prospect of accessing a treatment which the MHRA has licensed unless they purchase this privately. This will lead a to a two tier system that discriminates against those who are not able to pay for this.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	PrescQIPP CIC
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

We note that the committee has asked for considerable additional information from both the submitting company and NHS England.

We are therefore uncertain as to whether all the relevant evidence has been presented and taken into account.

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

Yes. We agree that the summaries are a reasonable interpretation of the evidence that has been considered thus far.

We have significant concerns about the high degree of uncertainties in both the clinical evidence and economic modelling and analysis.

We have considerable concerns about the safety and efficacy of lecanemab. Whilst the MHRA has granted a marketing authorisation in the UK, the CHMP considered that overall the benefits of treatment are not large enough to outweigh

the risks associated with lecanemab, and have to date refused to grant a license for use in the European Union.
https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi

Currently there is a lack of capacity and infrastructure in the NHS to ensure safe and equitable use of lecanemab. Significant investment in NHS services including infrastructure, staffing and training would be required to support safe and effective use.

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.

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.

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.

Section 1.1 – recommendations

We strongly agree with the proposed negative NICE recommendation at this time.

There is considerable uncertainty within the economic model, which has led the committee to make multiple requests for further information from the company and NHS England. Given this high level of uncertainty, we agree that lecanemab should not be recommended.

There are significant concerns around safety and efficacy, and lack of capacity and infrastructure in the NHS to ensure safe and equitable implementation.

We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs.

Section 3.3 – Treatment positioning of lecanemab

The development of diagnostic and treatment pathways required for safe and effective use of lecanemab will require significant time and investment.

Currently the NHS does not have sufficient capacity available in specialist monitoring services required for diagnosis, initiation and ongoing monitoring of treatment (MRI, PET-CT, lumbar puncture, genetic Testing).
The patient pathway and clinical responsibility for diagnosis, treatment and for ongoing monitoring for patients treated with lecanemab needs to be clear. Commissioning responsibility for providing care throughout the patients journey needs be defined, with a joined up approach to providing services to ensure patient safety.

Availability of PET-CT scanners is variable across different locations in England. Provision of these services will need to be commissioned and funded at a national level to ensure equity in access for patients. This would take considerable time and investment. The availability of a blood test for amyloid beta in the future may make the use of lecanemab a more cost effective and accessible treatment option.

There needs to be sufficient capacity within NHSE commissioned PET-CT scanning facilities for patients at both initiation and at follow up. Delay in available scans for individuals with moving amyloid plaques causing symptoms could make treatment decisions very difficult. There are significant patient safety concerns if the drug is continued when it should have been stopped.

Clarity on the service model and sector intended for administering lecanemab is required. Appropriate consideration is needed around the resources required for staffing, training and infrastructure required for safe administration of lecanemab. The drug is administered by I/V infusion over an hour, every 2 weeks, with 30 minutes of nursing time required per infusion. The guidance suggests the infusions would be given locally. Currently ICBs do not have the resources, infrastructure (including appropriate clinic space and the availability of emergency treatment for adverse drug reactions), or trained staff available to administer IV infusions in their mental health facilities. Likewise, existing infusion clinics providing a service in the acute setting do not have the capacity to provide a service on the scale required.

Local specialist centres for diagnosis, administration of treatment and monitoring need to be commissioned and funded at a national level to avoid variation in access to treatment and hence inequalities.

As this is a new and potentially large patient cohort, it could put considerable strain on already stretched mental health services. The impact on other mental health services users needs to be considered. There is a risk that incorporating this service into existing mental health services will adversely affect services to other mental health patients.

The impact of additional demand on specialised diagnostic service (MRI, PET-CT, lumbar puncture, genetic Testing) needs to be considered to ensure other patient groups are not unduly affected and disadvantaged including oncology, cardiology, and patients with other neurological conditions. Implementation of this TA could lead to increased demand and pressure on already challenged waiting lists for all treatment sectors. Robust assurance from NHSE, NICE and the current national contract holders for diagnostic scanning that they can meet the increased demand is required before this TA can be implemented.

Section 3.6 – Clinically meaningful treatment effect

Given that the treatment effect was small and less than 1 increment on the CDR-SB scale (0.5), and that it was unclear how heterogenous the results were, the answers to these additional questions are vital to understanding the clinical effectiveness of treatment.

This information is also required to help with the development of stopping rules, which may depend on the effects in different patient groups.

Section 3.14 – Stopping rules

Any future positive NICE recommendations need to include clearly defined stopping criteria based on efficacy as well as safety. The draft guideline acknowledges that currently there are no clear guidelines on how progression to moderate disease is defined.

In the absence of clear unambiguous stopping criteria from NICE, systems will apply different review and stopping rules, and some patients and relatives will understandably want to continue the drug beyond the intended stop date. This will result in variation in access to treatment, and worsen health inequalities.

Clear, unambiguous review and stopping criteria using objective assessment of disease severity using validated tools currently in use in the UK are required, to ensure that guidance is implemented consistently across all areas, and there is fair and equitable access for all patients.

It is vital that at the point treatment is initiated, patients and their relatives and carers understand that treatment will be stopped if the response to treatment does not meet pre-defined thresholds.

Section 3.17 – Infusion costs

We have significant concerns about the large variation in estimated infusion costs and it is unclear what figure was used in the health economic modelling.

Clarity is needed on the care setting and service administering treatment, and an appropriate HRG cost used for financial modelling

Section 3.18 – Private care costs

The ambiguity over the private care costs also creates more uncertainty over the costs used, and hence the cost-effectiveness evaluation.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Leeds and York Partnership NHS Foundation Trust
Location	Not provided
Conflict	No
Notes	
Comments on the DG:	
Has all of the relevant evidence been taken into account? Yes	

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 in respect of drug therapy, no in respect of biomarker testing; it would be achievable to manage these tests, within reasonable budgets, but current resource limitations make this challenging.

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; but there is risk of age discrimination if there was to be a cut-off for biomarker testing that limits access to drug treatment, but this is not contained within the guidance.

Section 1.1 – recommendations

Genetic testing not widely available at capacity that would be needed if this was approved.

Section 3.24 – Managed Access

This would be a reasonable next step if the evidence can be provided.

Section 3.18 – Private care costs

The financial cost of developing ARIA isn't explored here.

Section 3.22 – Uncertainty in the cost-effectiveness of the estimates

Agree with all of these proposals for analysis.

Section 3.25 – Equality and health inequality issues

This is a concern in respect of application in clinical practice where younger people are already coming forwards to request this treatment.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Not provided
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

I have a concern about the characterisation of Mild Cognitive Impairment due to Alzheimer's disease (with a positive amyloid test) as always being a precursor to Dementia due to Alzheimer's disease - as described in comments on the text selection within the guidance. This does not take into account the good evidence that this is often not the case and that numerous factors can influence the progression or resilience to dementia, even when there is evidence of the presence amyloid.

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

Yes. As a clinical expert in this area I agree with the committee's recommendation that there is insufficient evidence and experience with lecanemab to make it available for treatment of Mild Cognitive Impairment within the NHS.

Section 3.2 – Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease "The clinical experts emphasised that all people with MCI caused by Alzheimer's disease eventually progress to having dementia."

This statement is incorrect and should be amended. I wonder if it is a simple transcription error and should read "...experts emphasised that NOT all people with MCI caused by Alzheimer's disease eventually progress to dementia."

Many people with PET or CSF evidence of amyloid pathology and MCI will never go on to develop clinical dementia. 54-59% of amnestic MCI patients with a positive amyloid test had not progressed to dementia after 3 years (Wolk (2018), Vos (2015)). In post-mortem studies 20-39% of cognitively normal older people had amyloid pathology in the brain at death, but had never developed dementia (Boyle (2024), Bowles (2019), Robinson (2018), Schneider (2009)).

In people with MCI and a positive amyloid test many other possible contributing factors may increase or decrease their risk of progression to dementia. These contributing factors include vascular disease, poor sleep, poor hearing, low mood, drug effects, non-degenerative brain ageing, and metabolic effects of diabetes. Similarly, there are many factors that may confer resilience to progression of MCI, even in people with amyloid positivity, including social class, level of educational attainment, genetic resilience, high levels of social interaction and support, good cardiac health, and good nutrition. Many of these factors affecting both risk of progression and resilience are modifiable, and people with MCI may have, or may develop, sufficient resilience to further neuro-degeneration such that they never progress from MCI to dementia, even when there is on-going amyloid deposition in the brain.

Bowles E, Crane P, Walker R, Chubak J, LaCroix A, Anderson M, et al. Cognitive Resilience to Alzheimer's Disease Pathology in the Human Brain. JOURNAL OF ALZHEIMERS DISEASE. 2019;68:1071-83.

Boyle R, Townsend D, Klinger H, Scanlon C, Yuan Z, Coughlan G, et al. Identifying longitudinal cognitive resilience from cross-sectional amyloid, tau, and neurodegeneration. ALZHEIMERS RESEARCH & THERAPY. 2024;16.

Robinson J, Corrada M, Kovacs G, Dominique M, Caswell C, Xie S, et al. Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+Study. ACTA NEUROPATHOLOGICA. 2018;136:377-88.

Schneider J, Aggarwal N, Barnes L, Boyle P, Bennett D. The Neuropathology of Older Persons with and Without Dementia from Community versus Clinic Cohorts. JOURNAL OF ALZHEIMERS DISEASE. 2009;18:691-701.

Vos S, Verhey F, Frölich L, Kornhuber J, Wiltfang J, Maier W, et al. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. BRAIN. 2015;138:1327-38.

Wolk D, Sadowsky C, Safirstein B, Rinne J, Duara R, Perry R, et al. Use of Flutemetamol F18-Labeled Positron Emission Tomography and Other Biomarkers to Assess Risk of Clinical Progression in Patients With Amnestic Mild Cognitive Impairment. Jama Neurology. 2018;75(9):1114-23.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Alzheimer’s Disease International
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

We welcome the Committee’s acknowledgment of the high burden that dementia has on the UK, noting that dementia is the leading cause of death in the country (Office for National Statistics) with an estimated 944,000 people living with the condition within the UK (NHS). Alzheimer’s disease typically constitutes 60-70% of all dementias (WHO)

While we respect the committee’s decision and thank the committee for their thorough analysis of the proposal, as a federation of over 100 national Alzheimer and dementia associations from around the world, we represent many living with the condition who will affected by the decision taken by the NICE committee and thus be unable to access the treatment through the NHS. We note that this has been acknowledged by the committee under 3.26 Uncaptured Aspects

In light of the decision outlined in the committee papers and draft guidance and in the hope that this decision will be reconsidered we would like to highlight certain aspects of the committee’s analysis which we feel do not adequately represent the burden of dementia on society.

We note from 3.26 Uncaptured aspects in the draft guidance that “The impact on the finances and productivity of carers for people with Alzheimer’s disease were not captured in the model. The committee noted that these costs fall outside of the NICE reference case.” Given that the estimated costs of informal care are estimated to constitute 50% of the global cost of the condition (WHO), we strongly believe that these costs should be considered within the cost-effectiveness analysis. Indeed in the committee papers it is noted that “The annual social and informal care cost of dementia is currently £22.7 billion in the UK, with over 1.1 million 25 to 49 year-olds out of work due to caring responsibilities related to AD’”. This figure also does not account for the impact of care on the carer’s mental, physical and social wellbeing (Lindeza et al 2014) and the subsequent cost to the NHS. It is unclear to us, given the substantial cost and impact of informal care, why these have been excluded from cost estimates and we invite you to include them. To exclude carer burden does not provide an adequate reflection of the true cost of the condition.

We would also like to highlight the absence of any disease modifying therapy for Alzheimer’s disease and the impact that a negative recommendation is likely to have on the research and industrial sector in this space. From our engagement with people living with Alzheimer’s disease, many articulate that all they want is a simple choice, a choice to use a treatment which may delay their symptoms or alternatively, peruse non-pharmaceutical options. A treatment which is not effective for all eligible patients is commonplace in other disease areas such as oncology, where in addition multiple treatment options exist. This is in stark contrast to Alzheimer’s disease. While challenging to quantify, the determination of eligible patient populations does not reflect the total number of those who may actually utilise the medication, partially because of underdiagnosis, where we are also advocating for changes, as all of those seeking diagnosis should obtain one, but also because some living with dementia have articulated that they would not use these treatments, even if they were available.

Finally, as a global organisation we are concerned with the wider societal aspects of the broader decision to approve lecanemab for private treatment in the UK, but not for public access. As we have written in several public outlets, there is a tangible risk that with the EMA having refused approval of lecanemab, it will lead to those who can afford it travelling from Europe to seek treatment in England. This could create a two-tier society of have and have nots, which could have serious repercussions for the dementia community as a whole.

On the basis of all the above we invite you to reconsider the decision.

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

Please see above.

Draft guidance consultation

We welcome the Committee’s acknowledgment of the high burden that dementia has on the UK, noting that dementia is the leading cause of death in the country (Office for National Statistics) with an estimated 944,000 people living with the condition within the UK (NHS). Alzheimer’s disease typically constitutes 60-70% of all dementias (WHO)

While we respect the committee's decision and thank the committee for their thorough analysis of the proposal, as a federation of over 100 national Alzheimer and dementia associations from around the world, we represent many living with the condition who will affected by the decision taken by the NICE committee and thus be unable to access the treatment through the NHS. We note that this has been acknowledged by the committee under 3.26 Uncaptured Aspects

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On the basis of all the above we invite you to reconsider the decision.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Shropshire Telford and Wrekin ICB
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes

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

While lecanemab has shown some potential in addressing amyloid-beta plaques associated with Alzheimer's disease, the evidence regarding its long-term efficacy and impact on disease progression remains uncertain. Clinical trials have not conclusively demonstrated that lecanemab leads to significant and sustained cognitive improvements, especially when considering the variability in patient responses.

In conditions like Alzheimer's, where treatment outcomes can be difficult to measure and predict, it is crucial that any approved therapy provides clear and consistent benefits. We believe that approving a treatment without robust evidence of its efficacy could set a precedent that might lead to the adoption of other expensive, yet minimally effective, treatments. This could ultimately divert resources away from interventions that are proven to be more effective and equitable.

One of the key concerns with lecanemab is its high-cost relative to the uncertain clinical benefits. NICE's role in safeguarding NHS resources by ensuring that treatments are both effective and offer value for money is essential, particularly in a context of finite healthcare budgets. The rejection of lecanemab on cost-effectiveness grounds is a responsible decision that prioritises the allocation of resources to treatments and services that are demonstrably beneficial to patients. The approval of lecanemab could have significant financial implications, potentially requiring the NHS to allocate a substantial portion of its budget to a treatment with limited evidence of efficacy. These funds could instead be used to support a wide range of services that benefit a larger number of patients, including those with Alzheimer's disease through more holistic and supportive care approaches

2. Are the recommendations sound and a suitable basis for guidance to the NHS? Yes. The elements in question 1 should be considered when reviewing future treatments in this disease area.

3. 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?

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?

We believe that NICE's decision to reject lecanemab does not inherently result in discrimination against any specific group. The recommendation was based on a thorough assessment of clinical efficacy, safety, and cost-effectiveness, criteria that are applied uniformly across all treatments, irrespective of the demographics of the patients who may receive them. However, it is crucial to consider the broader context in which these decisions are implemented to ensure equity and fairness.

1. Age Considerations: Alzheimer's disease predominantly affects older adults, and there is a risk that any decision regarding treatment availability might disproportionately impact this age group. However, the rejection of lecanemab is rooted in concerns about its efficacy, safety, and cost-effectiveness rather than an age-related bias. To mitigate any potential age discrimination, it is essential to continue offering comprehensive support and alternative treatments to older patients and to ensure that age does not become a barrier to accessing other effective care options.

2. Disability Considerations: People living with Alzheimer's disease often face disabilities related to cognitive function. It is vital that the rejection of lecanemab does not limit access to other necessary services and supports that can help manage the disease's progression and improve quality of life. We recommend that NICE and healthcare providers ensure that decisions do not inadvertently reduce the availability of broader support services essential for this group.

3. Ethnic and Socioeconomic Considerations: There is a need to be aware of the potential for disparities in healthcare access among different ethnic and socioeconomic groups. These groups may already face barriers in accessing care, and it is important to ensure that the rejection of lecanemab does not exacerbate existing inequalities. We support the implementation of targeted outreach and support services to ensure that all patients, regardless of background, have access to the best available care.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	NHS BSW ICB
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

We note that the committee has asked for considerable additional information from both the submitting company and NHS England. We are therefore uncertain as to whether all the relevant evidence has been presented and taken into account.

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

Yes. We agree that the summaries are a reasonable interpretation of the evidence that has been considered thus far.

We have significant concerns about the high degree of uncertainties in both the clinical evidence and economic modelling and analysis.

We have considerable concerns about the safety and efficacy of lecanemab. Whilst the MHRA has granted a marketing authorisation in the UK, the CHMP considered that overall the benefits of treatment are not large enough to outweigh the risks associated with lecanemab, and have to date refused to grant a license for use in the European Union.
https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi

Currently there is a lack of capacity and infrastructure in the NHS to ensure safe and equitable use of lecanemab. Significant investment in NHS services including infrastructure, staffing and training would be required to support safe and effective use.

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.

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.

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?

No

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Not provided
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

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

No, I'm afraid not.

I. The inclusion of the cost of diagnostic measures in the ICER is extremely strange to a clinician that routinely uses molecular diagnostics in the *absence* of a disease modifying treatment. Diagnosis using CSF itself is recommended by the NICE 2016 guidance on dementia "where there is uncertainty in the diagnosis [subtype]". So, when is a diagnosis uncertain with respect to Alzheimer's? Beach et al (2012) and the IDEAS study (Rabinovici 2019) both prove that our subtype-diagnoses of Alzheimer's disease are incorrect (when clinico-pathological correltion is conducted) approximately 30% of the time. That unfortunately means that a diagnosis of Alzheimer's disease is ALWAYS uncertain, and likely ever more uncertain the earlier in the disease process someone presents with symptoms. So, 8 year-old NICE guidance is itself recommending molecular diagnostics in the vast majority of people who present with 'early dementia'. The fact that many clinicians diagnosing the disease *consider* themselves certain either because of hubris or a lack of understanding or scientific knowledge, or merely because they have no option because they lack access to molecular markers, is not relevant to whether or not NICE's evidence-based recommendations regarding diagnostics should stand.

However in the 2016 Guidance, NICE has not specified stages of disease before serious disability occurs. 'Early dementia' (in RCTs) is equated to a CDR score of 1. This CDR total score requires:
"Moderate memory loss; more marked for recent events; defect interferes with everyday activities" as well as two or more of: a difficulty functioning independently in community affairs, needing prompting for personal care, impaired function around the home, or difficulty in judgement and problem solving.
So, some (including, here, NICE) assume that in the context of lecanemab, NICE;s 2016 dementia guidance applies only to those with CDR >=1, with already very significant levels of disability. If that assumption is made, I would put it to the committee that if 2016 NICE guidance requires molecular diagnosis at this disease stage already, then the cost of diagnosis should be excluded from the ICER *at least* for those with "early Alzheimer dementia" as defined by a CDR of >=1.

However, even this would be a misrepresentation of existing guidance. For those with CDR scores less than 1, in order to qualify for further (CSF) investigation with a view to lecanemab prescription they would have to show an objective impairment on a commonly used cognitive assessment tool. This impairment correlates with a disability in higher functions including difficulties reading, problems learning new information, repetitiveness and rapid forgetfulness. This represents a considerable reduction in quality of life for the patient, burden for family and others, leads to social isolation and can lead to neglect of other health conditions. In ALL respects,

this meets the *scientific* definition of early dementia (any decline in Instrumental Activities of Daily Living (IADLs) notwithstanding the RCT lingua franca using CDR), and therefore these people should be considered to be included in the NICE 2016 recommendations regarding CSF testing. NICE has *not* elected to specifically use the CDR to exclude this level of impairment from its 2016 recommendations and did not include any specific measures (e.g. CDR) of functional disability to exclude less impaired people from those recommendations. Nowhere in the 2016 guidance are people with a total CDR = 0.5 specifically excluded, nor is that exclusion implied. An unconscious mapping appears to have occurred between the CDR and the standard definition of MCI (based on IADLs) which was not implied in the 2016 guidance.

Therefore, the inclusion of CSF diagnostic costs in the base case of the ICER represents a failure of NICE to recognise that these diagnostic tools (with the exception of the 10% estimated to require amyloid PET) are already required by the NICE 2016 guidance.

I conclude that diagnostics should be removed from the base case cost structure, as they are not a novel requirement for the use of lecanemab, but rather an existing component of the recommended diagnostic pathway for the vast majority of people who would be eligible for lecanemab. The fact that these diagnostics are currently underutilised is a symptom of massive under-investment in UK Mental Health Trusts. Including them in the calculation of the cost of lecanemab, resulting in the recommendation that it lacks cost-effectiveness, represents in lay terms a statement that: "we have failed to adequately fund and implement existing guidance, and therefore we are expecting any new treatment relying on the implementation of that guidance to cover both sets of costs". No novel treatment could *ever* meet such a standard.

II. The insistence of NHSE on the higher cost tariff for infusions (>£500 versus ~£200 suggested by expert clinicians and Eisai) is likely to significantly impact the ICER because of the frequency of infusions - with no evidence provided for the suggested "increased complexity" of giving infusions containing monoclonal antibodies (a powder suspended in saline) compared to giving cytotoxic chemotherapy (a powder often toxic to the skin which requires significantly more care and effort in the preparation and administration of the infusion, special utilities, refrigeration and pharmacy specialisation). NICE must re-estimate the ICER using the lower of the two tariffs for infusion to avoid the appearance of very significant bias in the application of its own rules. Having given similar mAbs in clinical trials, I can say their infusion is no more complex than an infusion of any other drug, and with respect to cytotoxic chemotherapy, significantly less so. Failing this, NICE should at the very least require NHSE to provide unrefutable evidence for its claim of higher complexity and therefore cost.

III. The assumption that an accurate early diagnosis will cost more per QALY is based on spurious assumptions. By diagnosing accurately and early, using CSF biomarkers, there is significant reduction in uncertainty and distress. People are better able to plan, prevent crises, and make choices about their own healthcare.

IV. No reference (outwith the company's submission) has been made to the LSE's economic modelling on cost-utility (Anderson et al https://www.lse.ac.uk/cpec/assets/documents/EconomicmodellingAD.pdf) commissioned by ARUK, which demonstrates the cost utility of a DMT which reduces "conversion" from MCI to dementia (i.e. CDR 0.5 to CDR 1) by 30% per year. NICE have accepted that lecanemab does this based on Clarity AD

evidence. " The benefit from deferring onset by one year is therefore about £28,000, other things being equal, if a QALY is valued at £20,000 (as represented by the willingness-to-pay threshold associated with NICE). It is therefore no surprise that the therapies considered in this paper would be cost-effective under the NICE threshold of £20,000 per QALY even at a substantial price and, given the incidence and prevalence of AD, that the impact of providing the therapies on decreasing NHS expenditure would be considerable."

V: The costs submitted by NHS England are not rigorous and err on the side of expense. (See II but further). APOE genotyping will not cost £250 per person at scale. A 2019 quote from a London-based supplier was £60 per test. Other suppliers would undoubtedly enter the market and push cost down. Some laboratory plasma assays are already available which would give proxy results with good sensitivity and specificity at the same time as CSF biomarker testing. These could easily be adopted and trialled over the course of a years-long managed access programme.

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

I don't believe so. I believe that the failure to provide a managed access option is a missed opportunity for the NHS to modernise diagnostic and therapeutic services for people living with the earliest stages of the diseases underlying dementia. The arguments presented that the ICER could not feasibly be brought down by this managed access program are not rigorous:

The "uncertainty" in the cost-utility estimates could easily be addressed using a managed access option with data collected within the sites included in Dementia Platforms UK's Trial Readiness Framework. This would be real-world data on people attending UK memory clinics. A list of the potential sites is here https://www.dementiasplatform.uk/trials-delivery/Trials-Delivery-Framework. It is *not* true that significant extra resource or investment would be needed to capture cognitive and side effects in a registry, as much of the infrastructure already exists, albeit in a formally "research" context, but with the aim of capturing real-world data.

Uncaptured aspects (3.26)
"The potential uncaptured costs of lecanemab raised were:
• false hope for people who are not eligible for lecanemab, or who may find out they are APOE4 carriers and may experience worse outcomes than others. "

In fact the REVEAL studies (https://www.genomes2people.org/research/reveal/publications/) conducted in the United States suggest this is not the case. People have transient anxiety after disclosure which is not sustained. Many people not suitable for lecanemab due to APOE4/4 status will be eligible for enrolment in clinical trials of medications with different mechanisms of action. In the context of risk assessment for lecanemab, these people already *know* they have molecularly defined Alzheimer's disease (at the stage when they get genetic testing) so any anxiety would be about transmission to children of one or more copies of the gene. With sensitive counselling, including communicating the evidence base around dementia prevention (Lancet Commission 2024) this need not be anxiogenic at all.

"false hope for people who believe that lecanemab is a cure for Alzheimer’s disease and not a treatment that slows disease progression"

This implies that there will be no pre-treatment counselling regarding the actual effect, including information in patient-facing material provided by the company, which very specifically details that the aim is to slow progression at the earliest stage. I'm afraid for any specialist working in this area, this is a spurious concern, bordering on the assumption of incompetence in an entire field.

" harmful effects of repeated diagnostic testing and monitoring"

I am a later life psychiatrist and regularly perform lumbar punctures. The rate of complications is exceptionally low, and patient comfort is a priority. With adequate doses of local anaesthetic the average discomfort experienced is rated by patients as 1-2/10. They find it very acceptable, and where results are equivocal, all are willing to come back at interval for further testing. I'm afraid again this is a spurious concern from outside the field.

"significant increase in demand for NHS primary and secondary care services that may affect the provision of other services"

In fact, if NICE allowed this drug into managed access tomorrow, very few people could access it and the real cost to the NHS would be very small. This is because only 0.13% of people attending UK memory clinics currently receive a biomarker-based diagnosis (RCPsych 2024 audit). Of these, 15% will be excluded because of APOE4/4 status, and more because of frailty, anticoagulation, or existing micro-haemorrhages on baseline MRI brain. It would take considerable time - years - to scale up current CSF biomarker testing, over which period valuable information about the real-terms costs, scalability, and utility of the medication would become available. It would be trivial to have patient complete (for example) both EQ5D and "Healthcare Utilisation in Dementia" questionnaires while having their infusions, and therefore it would be easy to build a 2-5 year picture of the impact of the drug on other services (initially minimal) and the potential cost of scaling to the whole NHS.

When disease-modifying treatments arrived for Multiple Sclerosis in the early 2000s, patients advocated for access, and the availability of disease-modifiers grew its speciality so that now there are for more specialist nurses, MS-ologists and dedicated services. Has this happened at the expense of other neurology services? Was it even a concern? It does speak to a considerable double standard in the assessment of potential disease modifying treatments when these kinds of comparisons are considered. It must instead be considered that lecanemab is the first step in the treatment of a complex, multistage, multi-pathology disease. It addresses one component of the disease, and neither the company nor experts in the field have claimed it is a silver bullet. Instead it is similar to Natalizumab (Tysabri) for MS, a drug with significant risks, all of which can be carefully mitigated, requiring an upskilling of the professions concerned, a challenge to which they will be delighted to rise. The first in a long line of potential treatment options.

"substantial investment in infrastructure and training for NHS care pathways to be redesigned to accommodate new treatments"

This is already underway at no extra cost to the NHS. The assumption of increased cost is untrue. In traditional pathways, people presenting with early disease are given a "diagnosis" of MCI and then sent away to "come back when you have dementia". They do, and thus are seen for separate diagnostic assessments at two points in time. Any modernised pathway with CSF based diagnostics gets to an

answer immediately, negating the second assessment. Thus, the (necessarily) very slow roll-out of lecanemab would allow a shift from "double assessment" to "definitive assessment". It is not at all clear that this would involve greater expense to the NHS or the UK. Indeed, if one costs in the interval between MCI and Dementia diagnosis: the anxiety about cognitive decline, the need for multiple sets of neuroimaging, the unexplained cognitive disability and the toll on loved ones, gradually becoming carers, the inability to plan and therefore prevent crises, the potential reduction in delirium (just for example) by knowing about underlying neurodegeneration and avoiding triggers, it is quite likely that definitive diagnosis would pay both for itself and any associated increase in infrastructure. However, it is necessary to measure such things, and the current health economic framework for dementia appears far too narrow to capture all the potential cost benefits.

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?

Yes, the use of the ICER measure relied upon by NICE discriminates against diseases of late onset, as diseases with earlier onset -especially those with a lifetime horizon - will always find it easier to meet the ICER threshold. This therefore discriminates against older people. While the ICER is "standard" and NICE must abide by its manual, there is clearly a case for reconsideration of the *threshold* in older people, especially where modelling suggests the ICER/Cost-per-QUALY could not feasibly be met by any novel complex therapy.

The ubiquitous reliance on the EQ5D-3L means that the changes of early Alzheimer's cannot be captured. These include wordfinding difficulties leading to social withdrawal; rapid forgetfulness leading to missed appointments, significant burden on friends and relatives as well as constant anxiety. Low mood is a frequent concomitant. However the EQ5D is focused on physical disability, lacks the resolution to detect small changes over time, and does not address the kinds of deficits and loss of life-quality associated with the subtle loss of higher cognitive functions. This, therefore, discriminates on the basis of the disability itself. Using the EQ5D as the currency of QALYs it is hard to imagine any complex treatment being able to meet NICE's arbitrary thresholds. Thus, discrimination is in fact baked-in to the assessment process for any mental condition not causing physical disability at a particular stage of disease. The EQ5D is also less suitable for older people. This has been recognised by studies such as the ELSA, which captured QOL using the CASP-19, much more suited to older populations. (See sections 4.3.10, 4.3.17 of the NICE HTA manual.)

The absence of a mapping function from QoL-AD to EQ5D is mentioned in the committee papers (B.3.4.2). A paper is referenced, and the fact that the algorithm code is inaccessible. However, the lead author Dr. Ines Rombach is at Sheffield now and I have contacted her for the Stata code implementing the mapping algorithm mentioned.

Section 3.25 reports: There is current inequality in terms of who has an Alzheimer’s disease diagnosis and accessing care. This will be exacerbated by introducing the complex diagnostic pathway for lecanemab.

There is no evidence for this statement. Is there evidence more complex diagnostic pathways in other diseases increase inequalities? In fact, the current pathway which sends people away because their diagnosis is unclear is much more

discriminatory against e.g. ethnically minoritised groups than any CSF molecular diagnostic pathway. For example, in the assessment of people for whom English is not a first language, commonly used pen-and-paper cognitive tests are invalid, and cannot adequately capture decline, resulting in greater uncertainty. CSF based molecular diagnostics however, can give a definitive result in these populations, long before cognitive decline has become serious enough to result in the stigmatisation and social isolation that commonly occurs in people with moderate to severe dementia in minoritised communities. Instead, it replaces the understanding of dementia as "inevitable" with ageing with instead a clear understanding of diseases of the brain as just that, diseases in which we can intervene. The statement is completely out of keeping with my experience as someone who has seen a radical improvement in diagnostic accuracy in the minoritised groups I see in clinic since the introduction of our CSF testing pathway.

Further, in the presence of a treatment and therefore definitive diagnostics, GPs may be more likely to refer on people with lower degrees of suspicion, and thus lower severities of cognitive impairment. This is likely to decrease the threshold of referral for people from minoritised communities in whom cognitive decline is sometimes associated with significant stigma.

"3.25: People with Down's syndrome (who have a more than 90% lifetime risk of developing Alzheimer's disease), people with young-onset dementia and people from diverse family backgrounds were not fully represented in Clarity AD. These groups are at risk of being excluded from accessing lecanemab"

These are different diseases, with genetic drivers, not sporadic late-onset AD. Not treating them as if they were the same disease is not "discrimination", it is very sensible science. Separate studies will be necessary to determine the effects of amyloid reduction in people living with Trisomy 21, Presenilin-1 mutations and other genetic drivers of brain amyloid accumulation. People living with Down syndrome require different assessment pathways, depending on their level of disability; neuroimaging plays a different role, they often need tailored cognitive assessments. Specialised assessment and treatment is necessary, not discriminatory. It may well be that people with Down syndrome respond significantly better - in fact - to drugs currently in phase III trials, like gamma secretase inhibitors. More studies are certainly needed, but to assume any one drug has to be able treat the spectrum of brain pathologies lumped together under the eponym "Alzheimer's disease" is a grave mistake.

"3.25: Lecanemab may have different treatment effectiveness and benefits for different subgroups based on age, sex and family background."

This is literally true of every medicine in the BNF. That's why the company are proposing APOE genetic testing, and it is why we do studies on licensed medications to answer questions that lead to more personalised decisions about healthcare. The concern seems positively fanciful when there is currently no treatment for this or any of the diseases underlying dementia. Seeking or expecting a "silver bullet" drug that slows all aspects of the neuropathology with no difference due to age, sex or family background is an attainable standard to set for a disease with no treatment.

"3.25: Lecanemab would need significant increases in NHS capacity for service delivery. Inequalities may increase as existing services that are already under strain would be needed to deliver the treatment."

Inequalities may also *decrease* as people with less education (for example) begin to learn that "dementia" is a treatable series of illnesses, and seek care earlier. Ditto people from minoritised backgrounds. Services are under strain because recruitment and retention are impaired by working conditions in chronically underfunded NHS mental health Trusts. The implementation of a modernised diagnostic pathway, with disease-focused diagnoses (rather than "staging" the nebulous catch-all "dementia") would just as likely result in increased recruitment, retention and job satisfaction for all concerned. The pressures of working in an area where the diseases causing disability are not even DIAGNOSED correctly, never mind treatable, is part of the reason that UK mental health trusts find it so difficult to recruti and retain staff in this field.

Section 3.4 – Treatment positioning of lecanemab

Diagnosis using CSF biomarkers is not just for prescribing purposes, it provides valuable certainty on prognosis to people living with the earliest stages of cognitive decline. CSF based diagnosis is available in Bristol, several London sites, Manchester, South Wales, Sheffield, Sussex and Belfast, and rolling out to other centres. While it is true that it has taken some time to get these kinds of diagnostic pathways up and running, they do exist and organisations like the Brain Health Coalition led by third sector partners the Alzheimer's Society and ARUK are playing a leading role in spreading knowledge and skills.

Unfortunately NICE's positon seems to be that the required changes are too difficult to implement and that the learned helplessness of the NHS will not be overcome. On the contrary, many of us are working to modernise diagnosis for those with early AD, with or without licensed disease-modifying medications.

Genetic testing for APOE4 status requires experience and skill, but is routine in many centres conducting trials. These centres have the expertise and skill to disclose results sensitively and can and are developing patient facing materials suitable for the disclosure of results, and working with national dementia charities to develop such materials. Specialist genetic counselling is not necessary, and indeed experienced neurogenetic counsellors I have consulted see it as well outside their remit. The REVEAL studies indicate that this can be achieved with minimal anxiety or distress.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Herts and West Essex ICB
Location	Not provided
Conflict	No
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

We are uncertain as to whether all the relevant evidence has been presented and taken into account because it is stated that the committee has asked for more information and data from both the manufacturers and from NHS England.

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

Yes, the summaries are a good interpretation of the evidence that has been considered thus far.

There are significant concerns about the uncertainties in the clinical evidence and in the economic modelling and analysis.

Although MHRA has granted a license to market lecanemab in the UK, the equivalent European body (CHMP) looked at the same data and considered that the benefits of treatment do not outweigh the risks associated with lecanemab, CHMP have refused to grant a license for lecanemab in the European Union. This is of concern for Commissioners, Clinicians and Patients

https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi

There is a lack of capacity and infrastructure in the NHS to ensure safe and equitable use of lecanemab. Significant investment in NHS services including infrastructure, staffing and training would be required to support safe and effective use. This would significantly inhibit implementation and result in inequity of access. Overall the benefits are marginal benefits and do not outweigh the patient risks and costs to the NHS. We agree that a negative recommendation is appropriate.
The economic analysis is complex. The assumptions need to be transparent in the NICE report. In the future, if there is a positive appraisal it would need to be clear for commissioners where each part of the workup of tests, iv treatment and patient assessment is funded/provided (NHSE, acute, testing facilities, primary care) so that business cases can be costed up for the appropriate service areas. It is very hard to prepare for these drugs operationally unless the details of where each part will occur is transparent in the guidance. This clarity is also essential for good governance and safety.

These drugs if approved are expected to be used in a cohort of patients who do not routinely consult for NHS care because their condition is mild. The NHS currently lacks the structure to implement use of an IV treatment for dementia at this time, and re-organising services to enable 2 weekly IV infusions, patient assessment and tests to be co-ordinated will be complex and requires significant organisational changes . It will be necessary to have clarity about responsibilities where the pathways are spread across organisations, for example who is responsible for monitoring and follow up if additional tests are required during treatment, and what the pathway is for patients once the treatment is stopped.

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

Yes. The marginal benefits demonstrated in clinical trials do not currently outweigh the risk to patients of side effects and costs to the NHS. A negative recommendation is correct at this time.

If NICE is to approve a disease modifying Alzheimers drug the future, it is vital that a suitable funding is made available to ensure system readiness. NICE must work with NHSE to ensure that there is a clear implementation plan. Dedicated funding must be agreed and in place before publishing a positive TA. It should be noted that patient expectations around these medicines are high. The expectation of patients and their relatives needs to be managed so 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 product safety, the uncertainty in clinical evidence, economic modelling and analysis. It will be impossible to afford these treatments on the NHS unless dedicated funding becomes available, for the intended potentially very large cohort and could result in more harm for patients. A negative recommendation should remain 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?

The negative recommendation does not. However, a positive recommendation would be impossible to implement in practice for the NHS, due to workforce, capacity and resource issues so will inadvertently lead to unlawful discrimination.

Section 1.1 – Recommendations

We agree with the negative NICE recommendation.
There is uncertainty within the economic model, which has led the committee to make several requests for further information from the company and NHS England. Given the current level of uncertainty, and the small benefits, we agree that lecanemab should not be recommended.

There are significant concerns around safety. The efficacy in trials shows a small effect. Clear stopping criteria and definitions of when dementia has progressed to such a stage that treatments should be withdrawn. These issues may lead to unequal access, if patients in different areas stop their treatments at differing times, because of uncertainty around when the drug should be stopped. There will certainly be patient and carer pressure to continue to prescribe even when the patient has progressed to mediate impairment, which is when NICE consider the drug should be stopped. The NHS lacks capacity and infrastructure to ensure safe and equitable implementation. The marginal benefits shown in clinical trials, the need for invasive monitoring, along with the safety concerns from the effects of the treatment do not make for a positive appraisal.

A very large cohort of individuals (5% of patients over 65 years of age in our area is 15,000 people), might qualify for treatment, and in addition we will have some cases who are under 65 with young onset dementia. It would require a dedicated service of trained staff to deliver both the invasive tests (some of which are not currently easily available) along with IV administration every 2 weeks, and regular assessment of benefits versus stopping the drug. There will be an unseen burden on primary care in identifying and referring a large new cohort of patients, at a time when primary care is struggling with their existing workload. The current cognitive/memory assessment services could not cope with the new demand for their services. Once referred into a new service, the drug, staff, estates, infrastructure and monitoring costs to the NHS would be very significant, and could not be afforded locally without central funding to support use. An estimate if 30% of patients with mild cognitive impairment want this treatment is that the costs would exceed £100M in year one for our ICB, costs will increase annually if more patients are added in, unless clear stopping criteria are agreed. If there is no dedicated funding the costs of treatment, along with staffing, estates and monitoring are likely to lead to adverse changes to other mental health services, in order for these medicines to be afforded.

Section 3.4 – Treatment positioning of lecanemab

The diagnostic and treatment pathways required for safe and effective use of lecanemab will require significant change which will include time, training of staff and investment in the drug, tests, estates and additional staff. Overall the costs would be very high and the benefits of the drug are small.

The NHS does not have capacity available in the specialist monitoring services required for diagnosis, initiation and ongoing monitoring of treatment (MRI, PET-CT, lumbar puncture, genetic testing).

The patient pathway and clinical responsibilities for diagnosis, for treatment and for ongoing monitoring for patients treated with lecanemab needs to be absolutely clear. Commissioning responsibility for providing care throughout the patients journey needs be defined, with a joined-up approach across organisations (such as NHSE and ICBs) to providing services to ensure patient safety.

In our area, we only have PET-CT tests available for use in Cancer patients in three specialised centres (West Herts, North Herts and Mount Vernon) and there is no capacity to expand their use for MCI patients within our ICB. Some patients go out of area for these scans e.g. to London and Southend. Availability of PET-CT scanners is variable across different locations in England. Provision of these services will need to be commissioned and funded at a national level to ensure equity in access for patients. This would take considerable time and investment. The availability of a blood test for amyloid beta could make the monitoring to support use of lecanemab a more cost effective and accessible treatment option, but it is not available currently.

There needs to be sufficient capacity within NHSE commissioned PET-CT scanning facilities for patients at both initiation and at follow up. Delay in available scans for individuals with moving amyloid plaques causing symptoms could make treatment decisions very difficult. There are significant patient safety concerns if the drug is continued when it should have been stopped.

Clarity on the service model and sector intended for administering lecanemab is required. Consideration is needed around the resources required for staffing, training and infrastructure required for safe administration of lecanemab. The drug is administered by I/V infusion over an hour, every 2 weeks, with 30 minutes of nursing time required per infusion. The guidance suggests the infusions would be given locally. Currently ICBs do not have the resources, infrastructure (including appropriate clinic space and the availability of emergency treatment for adverse drug reactions), or trained staff available to administer IV infusions in their mental health facilities. Existing infusion clinics providing a service in the acute or intermediate care settings do not have the capacity to provide a service on the scale required.

To practically implement this pathway dedicated centres for diagnosis, administration of treatment and monitoring need to be commissioned and funded at a national level to avoid variation in access to treatment and hence inequalities .

This is a new and potentially large patient cohort. Seeing these patients could not be subsumed by the existing mental health services. We have concluded there would need to be a new stand-alone local service which would not be cost effective. The impact of this service on existing memory assessment clinics and

how patients move between services (as their condition worsens and so they no longer qualify for the disease modifying treatments) needs to be considered. There is a risk that incorporating many new patients into the existing memory assessment clinics or into other existing mental health services will adversely affect services to other mental health patients, because the current service would need to expand capacity very significantly. It will need to be clear where patients should be discharged to, and monitored, after their IV treatment. Ongoing monitoring will add to the caseloads of Primary Care/ Mental health service. We expect access to this drug is likely (over time) to increase numbers who enter the NHS for care of moderate and severe dementia phases as well as for mild cognitive impairment, with knock on impacts to the whole service for dementia and for primary care.

Increased access & equitable access to tests: Additional demand on specialised diagnostic service (MRI, PET-CT, lumbar puncture, genetic testing) needs to be considered to ensure other patient groups are not disadvantaged, for example cancer, cardiology, and neurology patients. If this NICE technical appraisal became positive this would cause increased demand and significant pressures on waiting lists for tests. We need assurance from the current national contract holders for diagnostic scanning, (and from NHSE and NICE) that there is capacity to meet the increased demand caused by the tests needed as work up and for urgent monitoring relating to side effects for lecanemab.

Section 3.6 – Clinically meaningful treatment effect

The treatment effect was less than 1 increment on the CDR-SB scale (0.5), which is usually agreed by clinicians to be too small to be clinically meaningful for the majority of patients. It was unclear how heterogenous the results were, and what happens to patients when treatments are withdrawn.
The answers to these additional questions are vital to understanding the clinical effectiveness of treatment. This information is also required to help with the development of national stopping rules, which may depend on the effects in different patient groups. Clear ways of scoring patients as having progressed to moderate dementia so that stopping is consistent nationally need to be agreed or developed by NICE.

Section 3.14 – Stopping rules

If NICE were considering making a positive recommendation, they need to include in the NICE TA clearly defined stopping criteria. The draft guideline acknowledges that currently there are no clear guidelines on how progression to moderate disease is defined which means that there will be pressure from patients and relatives to continue medication when the MCI has progressed to moderate.
If there are not clear stopping criteria agreed by NICE, systems will apply different stopping rules, and some patients and relatives will understandably want to continue the drug beyond the intended stop date. This will result in variation in access to treatment, and this will worsen health inequalities.

Stopping criteria which can be used in the UK by using an objective, numerical, assessment of disease severity is required, to ensure that guidance is implemented consistently across England, so there is fair & equitable access for all patients. Without clear rules on stopping treatments there could be inequitable access to treatment, which varies in different areas.

When treatment is initiated, patients and their relatives/carers will need to

understand that treatment will be stopped if the response to treatment does not meet pre-defined thresholds or if stopping criteria are met. There is an educational piece needed for the public, which we believe should be run nationally by NHSE, around the minimal benefits and the potential hazards of these treatments in order to prevent a huge influx of consultations into primary care by the worried well, blocking access to GP appointments for patients with other conditions, and causing unintended consequences to healthcare in all NHS sectors.

Section 3.17 – Infusion costs

There are large variations in potential infusion costs, which vary depending on the setting, and the cost of administration is currently not agreed between NICE and the company who make it. It is unclear what figure will be used in the health economic modelling used by NICE. Clarity is needed on the care setting where treatment is given IV, and the required monitoring and observation periods, then an appropriate HRG cost can be used for the financial modelling. We agree that the monitoring which is required may be more complex than that used for routine chemotherapy, given the side effect profile, and unlike chemotherapy, we do not think that this new drug will be suitable for home IV administration until there is a lot more experience with its use and the common acute side effects.

Our local mental health services do not currently administer infusions, therefore new estate, staffing capacity and training for staff will be needed.

Setting up services which talk to each robustly is a challenge, if patients go to different services for Tests, infusions and for assessment of their condition. Cross referral between systems needs to be timely to ensure safety; for example if side effects mean urgent tests are needed, or when infusions are stopped.

Over time, having a treatment for MCI will change the size of our dementia patient case load.

Additional resources will be needed in existing services for moderate and severe dementia, for use by and assessment of patients who stop lecanemab. Stopping lecanemab may be because of side effects or because they meet the agreed NICE stopping criteria.

Section 3.18 – Private care costs

The size of the private costs may be affected by whether this drug is approved or declined by NICE, which makes this aspect hard to model. Ambiguity over the private care costs creates additional uncertainty over the costs used, and hence the cost-effectiveness evaluation.

It should be noted that our clinicians believe that if patients access the drug privately and get side effects then the NHS may need to see these patients urgently to assess them, if their side effects are acute. This will add additional NHS costs even if the drug remains a negative assessment by NICE.

Access to PEP-CT tests is not easily found for private care, and concerns have been raised that this may take away PEP-CT capacity from the NHS.

We do not know the impact of stopping the drug suddenly at this time, on the symptoms, but stopping treatment suddenly will happen if the patient cannot continue to pay for private services.

It would be helpful if a register of private users outcomes and side effects could add to our knowledge about these treatments.

Name	[redacted]
Role	Not provided
Other role	Not provided
Organisation	Not provided
Location	Not provided
Conflict	No
Notes	

Comments on the DG:

As an individual I am thankful to be able to comment on my thoughts for the approval of lecanemab on the NHS.

I was devastated, crying when I heard NICE wasn't approving lecanemab for the NHS.

Lecanemab is such a positive, giant step for finding a cure for Alzheimer's.
I understand all the negatives of this drug-cost and 'little' improvement. However it is a massive step that has taken 20+ years to get here. It needs to be given the go ahead. It would start out as being for the very few anyway as things such as diagnosis need to be speeded up. Whilst the few are on this drug, more will be learnt, the supplier would hopefully lower the price, most importantly people would be given hope. There are more, possibly better drugs following up but this one being the pioneer should be given the go ahead. Please, please we have to start NOW. How can dementia, the UK's biggest killer, be so far behind in the world of medicine? Because drugs like this aren't given the chance. So few have really trialled this drug, we have small results in what could be a much brighter outcome. It really is breaking my heart. I'm extremely sure my plea would go nowhere in making a change, but thank you for hearing my desperate voice. In the meantime Alzheimer's will continue to devastate families lives.

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 consultation – Additional evidence

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1. Additional clinical evidence

1.1 Clinical effectiveness results from Clarity AD – ITT excluding *APOE4* homozygotes

Marketing authorisation for lecanemab was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) on 22nd August 2024. Lecanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε4 (*APOE4*) heterozygotes or non-carriers.[1] The company have provided results, from Clarity AD, for the indicated population.[2]

1.1.1 Primary efficacy outcome CDR-SB

Table 1.1: Change from baseline in CDR-SB Score at 18 Months – MMRM – ITT excluding *APOE4*

CDR-SB	**Lecanemab (n=723)**	**Placebo (n=743)**
Number of patients included in the MMRM	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	1.151 ([redacted])	1.730 ([redacted])
Adjusted mean difference in change from baseline (lecanemab – placebo)	-0.579	
95% CI for differences	-0.811, -0.347	
p-value	<0.00001	
% Difference vs. placebo	-33%	
Based on Table 2, Response to DG Appendix[2] CDR-SB = Clinical Dementia Rating - Sum of Boxes; CI = confidence interval; MMRM = mixed model for repeated measures; SE = standard error; ITT = intention-to-treat		

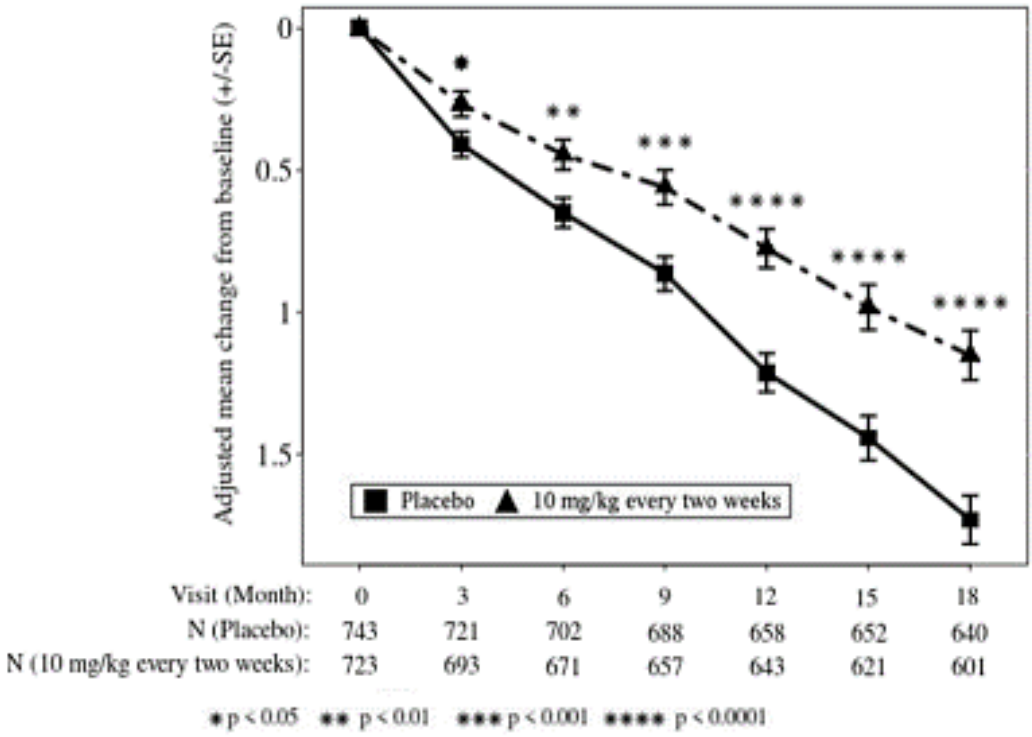
Table 1.2: Adjusted mean difference versus placebo in CDR-SB by domain

Domain		**Lecanemab (n=723)**	**Placebo (n=743)**
Week 79, n		[redacted]	[redacted]
Memory	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Orientation	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	

Judgement problem solving	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Community affairs	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Home and hobbies	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Personal care	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	

Based on Table 1, Response to DG Appendix[2]
CDR-SB = Clinical Dementia Rating–Sum of Boxes; CI = confidence interval; SE = Standard error

Figure 1.1: Adjusted mean change (±SE) from baseline in CDR-SB – ITT excluding *APOE4*



Visit (Month):	0	3	6	9	12	15	18
N (Placebo):	743	721	702	688	658	652	640
N (10 mg/kg every two weeks):	723	693	671	657	643	621	601

Based on Figure 1, Response to DG Appendix[2]
CDR-SB = Clinical Dementia Rating – Sum of Boxes; kg = kilogram; mg = milligram; SE = standard error

Figure 1.2: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population

Based on Figure 13, Response to DG Appendix[2]
APOE4 = Apolipoprotein E4; CDR-SB = Clinical dementia rating – sum of boxes; ITT = intent-to-treat; RR = relative risk difference from placebo

Figure 1.3: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, age < 65 years

Based on Figure 14, Response to DG Appendix[2]
CDR-SB = Clinical dementia rating – sum of boxes; RR = relative risk difference from placebo

Figure 1.4: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, age 65 to 75 years

Based on Figure 15, Response to DG Appendix[2]
CDR-SB = Clinical dementia rating – sum of boxes; RR = relative risk difference from placebo

Figure 1.5: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months - indicated population, age ≥ 75 years

Based on Figure 16, Response to DG Appendix[2]
CDR-SB = Clinical dementia rating – sum of boxes; RR = relative risk difference from placebo

Figure 1.6: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, *APOE4* non-carriers

Based on Figure 17, Response to DG Appendix[2]
APOE4 = Apolipoprotein E4; CDR-SB = Clinical dementia rating – sum of boxes; RR = relative risk difference from placebo

Figure 1.7: Proportion of patients with CDR-SB cognitive and/or functional worsening by 18 months – indicated population, *APOE4* heterozygotes

Based on Figure 18, Response to DG Appendix[2]
APOE4 = Apolipoprotein E4; CDR-SB = Clinical dementia rating – sum of boxes; RR = relative risk difference from placebo

EAG comment: The EAG notes that: '*The committee concluded that lecanemab had a clinically significant treatment effect. But, it noted that the treatment effect was small and less than 1 increment on the CDR-SB scale (0.5).'*[3] The EAG considers that adjusted mean between group difference in change from baseline for the indicated population (excluding *APOE4* homozygotes), though slightly larger, is broadly comparable to that reported, in the original CS, for the ITT FAS+ population, -0.451 (95% CI: -0.669 to -0.233).[4]

EAG comment: The committee requested provision of the mean difference from baseline by treatment arm at 18 months for the 6 individual domains of CDR-SB; these data were provided by the company and are reproduced in Table 1.2. The committee also requested provision of the distribution of change in CDR-SB score from baseline at 18 months, compared for lecanemab and placebo arms; additional information has been provided by the company (Figures 1.2 to 1.7).[2] The company stated that: *'Overall, these results demonstrate a consistent treatment effect of lecanemab across CDR-SB domains and levels of cognitive and/or functional worsening by 18 months in the indicated population and in APOE4 and age subgroups. Therefore, the company do not consider the results to be heterogeneous.'*[5] The EAG agrees that these results support the presence of a treatment effect of lecanemab across CDR-SB domains and levels of cognitive and/or functional worsening, but note that there is some variation in the size of the observed effect.

Figure 1.8: Adjusted mean change (±SE) from baseline in CDR-SB (OLE)

Based on Figure 12, Response to DG Appendix[2]
Note: the delayed start group is the black line, which at 18 months changes to green to represent patients moving onto treatment with lecanemab.
AD = Alzheimer's disease; ADNI Alzheimer's Disease Neuroimaging Initiative; CDR-SB = Clinical Dementia Rating – Sum of Boxes; kg = kilogram; mg = milligram

EAG comment: The EAG notes that, from visual examination of Figure 1.8, there appears to be an acceleration of decline after the 18-month time point (OLE), but that this acceleration appears to be common to both lecanemab-treated and untreated (ADNI) patients, such that the treatment effect of lecanemab appears to be maintained at 36 months. At 36 months, lecanemab showed an absolute treatment difference in CDR-SB of [redacted] in the early start group compared to ADNI.

1.1.2 Secondary efficacy outcomes

The company have also provided results, for secondary efficacy outcomes from Clarity AD, for the indicated population.[2]

The adjusted mean difference (MMRM) in ADAS-Cog14, for lecanemab compared to placebo at 18 months, was -1.633 (95% CI: -2.555 to – 0.712), with a difference vs. placebo of -28%.[2] The adjusted mean difference (MMRM) in ADCOMS, for lecanemab compared to placebo at 18 months, was [redacted], with a difference vs. placebo of [redacted].[2] The adjusted mean difference (MMRM) in ADCS MCI-ADL, for lecanemab compared to placebo at 18 months, was 2.234 (95% CI: 1.342 to 3.126), with a difference vs. placebo of -39%.[2]

EAG comment: The EAG notes that the exclusion of *APOE4* homozygotes from the analyses consistently resulted in slightly larger effect size estimates than those reported for the ITT FAS+ population.

1.1.3 Exploratory outcome: Time to worsening of Global CDR score at 18 months

At 18 months, lecanemab showed a statistically significant reduction in the risk of progression to the next stage of AD on the global CDR score, hazard ratio (HR) [redacted] (95% CI [redacted]).[2]

EAG comment: The EAG notes that this HR [redacted] that reported, in the original CS, for the ITT FAS+ population, 0.69 (95% CI: 0.57 to 0.83).[4]

1.1.4 Health related quality of life

In the draft guidance, the committee requested provision of least-squares mean change from baseline in EQ-5D-5L health-related quality-of-life values, by treatment arm, analysed using a mixed effects model with repeated measures.[3] The company clarified that EQ-5D utilities analysed using MMRM had already been provided and queried whether the committee would like to see the adjusted mean change; it was confirmed that the adjusted mean change from baseline in EQ-5D-3L utilities was appropriate.[5]

MMRM were fitted to provide estimates of health state utility adjusted for factors that may influence the outcome in the modified population, these were: treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.[2] A detailed outline of utility values used for each health state, sources, and corresponding justification, the company provided these in Table 42 of Appendix A.2.5. The adjusted mean change from baseline in EQ-5D-3L utility values, analysed using a MMRM, are presented in Table 1.3 and Figures 1.9 to 1.11.

Table 1.3: Adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM

Sub-category		**Lecanemab (N=723)**	**Placebo (N=743)**
Patient reported	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Patient-by-Proxy	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	
Study partner	N	[redacted]	[redacted]
	Adjusted mean (SE)	[redacted]	[redacted]
	Adjusted mean difference: lecanemab-placebo	[redacted]	
	95% CI	[redacted]	
	P-value	[redacted]	
	% difference vs placebo	[redacted]	

Based on Table 9, Response to DG Appendix[2]
CI = confidence interval; MMRM = mixed model for repeated measures; n = number of patients in treatment group; N = number of patients at each visit; SE = standard error

Figure 1.9: Plot of adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM – patient reported

Based on Figure 9, Response to DG Appendix[2]
MMRM = mixed model for repeated measures; SE = standard error

Figure 1.10: Plot of adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM – patient-by-proxy

Based on Figure 10, Response to DG Appendix[2]
MMRM = mixed model for repeated measures; SE = standard error

Figure 1.11: Plot of adjusted mean change from baseline in EQ-5D-3L utility values at 18 months – MMRM – study partner

Based on Figure 11, Response to DG Appendix[2]
MMRM = mixed model for repeated measures; SE = standard error

EAG comment:

In response the company submission addendum (22nd April 2024), the EAG highlighted that, whilst the methods used by the company were generally considered reasonable, diagnostics were not provided and could thus not be assessed by the EAG.

Particularly, the EAG highlighted the following:

- linearity of relationships between the predictors and the outcome variable
- normality of the errors, homogeneity of error variance (homoscedasticity)
- independence, i.e. effects associated with the random variable groups are uncorrelated with the means of the fixed effect from the random variable groups
- model specification – the model should be properly specified (including all relevant variables and excluding irrelevant variables)
- examining individual observations that exert undue influence on the coefficients multicollinearity

Further, the EAG highlighted that it is unclear how utility values (Table 15 of the company's addendum) are exactly calculated (e.g. whether the Geographical region – Europe covariate is included in the calculation). The EAG notes that there exist slight discrepancies between HSUVs reported in Table 11 of the submission addendum, and those provided in Table 42 of the response to DG appendices.[2] The reason for which is unclear. Further, despite the provision coefficients for included fixed effects variables, it remains unclear exactly how utility values are calculated. The company specify that treatment-dependent utilities are factored into HSUVs, however, it is unclear whether Geographical Region – Europe and APOE4 carrier status were factored into the calculation.

The MMRM assumes that missing data is missing at random. No missing data imputation was performed. When highlighting the method for estimating and applying utility values in the EAG report (HRQoL EAG comment a), the EAG also noted that justification should be provided for the decision not to perform any missing data imputation.[6] No justification was provided and thus, it remains unclear whether the missing data is missing at random. If data cannot reasonably be assumed

to be missing at random, no imputation risks biasing the utility output of the MMRM and thus, imputation should be considered.

For the MCI due to AD and Mild AD health states, the CS and EAG base-case utilised self-reported patient HSUVs, with patient-by-proxy utilities for later health states. When implementing the MMRM, the company adopted patient-by-proxy utilities for all health states. The company suggest that these were utilised to address counter-intuitive patient-reported utilities (mild AD utility greater than MCI due to AD utility: fixed effects estimate of [redacted] for MCI due to AD vs moderate AD compared with [redacted] for mild AD vs moderate AD). While the committee noted that there was evidence to suggest poor agreement between self-reported vs carer proxy health related quality of life estimates, they expressed concerns that self-reported measurements may not accurately reflect quality of life as people adapt to the symptoms of their condition. The company, following a hand search exploring adaptation for AD, concluded that the concept is not well understood, leading to the understanding of what this would mean for proxy utilities being inconclusive. Nonetheless, the company conducted a scenario utilising self-reported utilities for MCI due to AD and mild AD health states. The results show an [redacted] in the ICER by [redacted]. In line with the EAG response to the company addendum and expert opinion presented in the CS, the EAG would prefer the use of patient-reported EQ-5D for MCI due to AD and Mild AD health states. However, the EAG does recognise the counter-intuitive results and the minimal impact on the ICER. The EAG recommends removing the fixed effects covariate for treatment. This approach would be in-line with the backwards elimination process utilised, adopting an α=0.05, as is commonly used.

1.1.5 Adverse events

The company provided revised safety data for the population of interest (excluding *APOE4* homozygotes).[2]

Table 1.4: Adverse event overview, core study (Clarity AD, SAS excluding *APOE4* homozygotes)

Category	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
TEAEs	[redacted]	[redacted]
Treatment-related TEAEs[a]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]
Deaths[b]	[redacted]	[redacted]
Other SAEs[c]	[redacted]	[redacted]
Life threatening	[redacted]	[redacted]
Requires inpatient hospitalisation or prolongation of existing hospitalisation	[redacted]	[redacted]
Persistent or significant disability or incapacity	[redacted]	[redacted]
Congenital anomaly/birth defect	[redacted]	[redacted]
Important medical events	[redacted]	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]	[redacted]
TEAEs leading to study drug withdrawal	[redacted]	[redacted]
TEAEs leading to study drug dose interruption	[redacted]	[redacted]
TEAEs leading to infusion interruption	[redacted]	[redacted]
TEAEs of special interest	[redacted]	[redacted]

Based on Table 13, Response to DG Appendix[2]

[a]Includes TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality

[b]Includes all patients with SAE resulting in death

[c]Includes patients with nonfatal SAEs only. If a patient had both fatal and nonfatal SAEs, the patient is counted in the previous fatal row and is not counted in the nonfatal row

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in treatment group; SAE = serious adverse event; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse event

Table 1.5: Treatment-emergent adverse events of special interest, core (Clarity AD, SAS excluding *APOE4* homozygotes)

Preferred term	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
Patients with any TEAE of special interest	[redacted]	[redacted]
ARIA-E	67 (8.9)	10 (1.3)
ARIA-H	98 (12.9)	52 (6.8)
Macrohaemorrhage	[redacted]	[redacted]
Superficial siderosis	[redacted]	[redacted]
Cerebral microhaemorrhage	[redacted]	[redacted]
Infusion-related reactions	[redacted]	[redacted]

Preferred term	Number of patients, n (%)	
	Lecanemab (n=757)	Placebo (n=764)
Skin rash	[redacted]	[redacted]
Other hypersensitivity	[redacted]	[redacted]
Suicidal behaviour	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]

Based on Table 14, Response to DG Appendix[2]
ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n = number of patients in treatment group; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse events

Most treatment-emergent ARIA-E were radiographically mild (lecanemab: [redacted]) to moderate (lecanemab: [redacted]) in severity. There was [redacted] categorised as having radiographically severe ARIA-E in the lecanemab arm and no patients in the placebo arm. Most treatment-emergent ARIA-E in the lecanemab arm were asymptomatic ([redacted]), whilst all ARIA-E were asymptomatic in the placebo arm.[2]

Most treatment-emergent isolated ARIA-H were radiographically mild (lecanemab: [redacted]. There were [redacted] radiographically moderate isolated ARIA-H and [redacted] radiographically severe isolated ARIA-H in the lecanemab arm. [redacted] had radiographically moderate isolated ARIA-H and [redacted] had radiographically severe isolated ARIA-H in the placebo arm.[2]

Most infusion-related reactions were mild or moderate in severity, with Grade 1 (lecanemab: [redacted] placebo: [redacted] and Grade 2 (lecanemab: [redacted] placebo: [redacted]. No patients in the placebo arm reported Grade 3 or 4 infusion-related reactions. In the lecanemab arm, [redacted] and [redacted] patients reported Grade 3 and Grade 4 infusion-related reactions, respectively; all [redacted] patients were discontinued from study treatment and did not receive subsequent infusions.[2]

EAG comment: The EAG notes that these data appear consistent with the summary of treatment-emergent ARIA-E and ARIA-H by *ApoE4* genotype provided in the EAG report (Table 3.37).[6]

2. Additional Economic Evidence and Updated Cost-Effectiveness Results

2.1 Summary and critique of company's changes compared with the ACM 1 company base-case

2.1.1 The company's updated base-case

While the company's new base-case could not be exactly reproduced using the old model file, the EAG believes that it came reasonably close without changing input parameters pertaining to the multistate survival model. The company upon request also provided a detailed description of all model changes with locations in the model and justifications. The EAG is satisfied that the company's updated base-case is doing what the company described.

Changes to the model include:

- Corrected lecanemab monitoring costs
- Update to the indicated population
- Removal of serious AEs
- EAG's preferred baseline proportions of MCI due to AD and mild AD
- Multistate survival model
- Mortality HR for MCI due to AD: 0.63
- Caregiver QoL modelled as utility increments
- Inclusion of *APOE4* testing for all patients tested (including *APOE4* homozygotes)
- Lecanemab administration cost source: micro-costing study
- Revised PAS

The EAG notes that the updated ICER is significantly reduced, which is caused mainly by the focus on *APOE4* non-carriers and heterozygotes subgroups (in line with the marketing authorization), the revised PAS, modelling caregiver QoL as utility increments (not requested by EAG or committee, but the 'carer QALY trap' was highlighted in the draft guidance and is addressed by this), and applying a weighted discontinuation rate to MCI and mild AD patients (not requested by EAG or committee) when changing the baseline proportions of patients in these states, as well as using the Crowell et al.[7] mortality HR of 0.63 for patients in the MCI state (not requested by EAG or committee). EAG changes to the company model prior to ACM1 that have not been used in this new submission include:

- Off-tx mild/MCI states should have SoC transitions: this relates to treatment effect waning and is addressed below
- Disable severity-based stopping rule: the company instead provided additional arguments for how this stopping rule can be operationalised, which is critiqued below
- Mortality HR in MCI set to 1: as mentioned above, the company reintroduced the Crowell et al.[7] mortality hazard ratio (critiqued below)
- Treatment-independent utility values: the company used a mixed methods repeated measurement model (critiqued below)
- Disable caregiver institutionalisation disutility: the company did not use the EAG's setting and this is critiqued below
- Use of NHS cost model assumptions: the company provided an alternative costing, which is critiqued below

Draft guidance committee preferences that have not been used include that the institutionalisation-based stopping rule should be disabled.

2.1.2 Effectiveness

2.1.2.1 Transition probabilities (Comment 6)

The company used the multistate survival model in its base-case, acknowledging the time dependency of transition probabilities as observed in the smoothed hazard plots for the indicated population (Appendix Figure 23).[2] The company furthermore responded to the EAG's concern about the original company model's handling of competing risks in converting transition probabilities from the end of the trial period to monthly transition probabilities in the model. The company explained that *"the multistate survival model implicitly handles competing risks as patients may either make the transition of interest (i.e., experience an 'event'), be censored at the end of the study, or be censored when they experience a movement to a competing health state. As such, patients are not censored from the entire analysis, only from one of the possible transitions. After a competing event occurs, patients contribute to the risk of making a different transition. For instance, a patient who transitions from mild AD to moderate AD would then contribute to the analysis for the moderate AD to mild AD transition. Thus, the multistate model appropriately handles competing risks."* The company consequently did not provide the Gidwani et al.[8] solution that was requested by the committee. The EAG considers that the company's approach addresses time-dependency and competing risks, but also notes that there are remaining doubts about the resulting health state occupancy when compared to that observed in Clarity AD (see Section on Validation below).

In addition, the EAG note that with the implementation of the multistate model, transitions to the severe health states were not estimated due to lack of data. For the transition from MCI due to AD to the severe health state, the company assumed a probability of [redacted] for both lecanemab and standard of care. For the transition from mild AD to severe AD, the company assumed that the transition probability from Potashman et al.[9] holds for standard of care, and applies a hazard ratio to this transition probability. The EAG notes that no justification was given for the assumption of a treatment effect on this transition and sets this hazard ratio to 1 in the EAG base-case.

As part of the new multistate survival analysis and in line with committee preferences, the company continues to allow backward transitions in their model and the EAG agrees that this is appropriate.

2.1.2.1.1 Estimation and selection of multistate survival models

The company provided a new multistate survival analysis for which APOE4 homozygotes were excluded (in line with the marketing authorisation). In the base case, the multistate survival model uses data from the Clarity AD core study period (0-18 months). Survival models were chosen based on statistical and visual fit as well as the appropriateness of the hazard pattern over time. For transitions:

1. MCI due to AD to mild AD
2. mild AD to moderate AD
3. mild AD to MCI due to AD
4. moderate AD to mild AD

A joint (i.e., dependent) modelling approach was used, in which the treatment effect was represented by a covariate within the survival model for each transition and assumed to be constant on the associated scale. This approach, assuming proportional hazards, was supported by the smoothed hazard plots that showed parallel hazards in general. The EAG broadly agreed with this but noted crossing hazard rates

over time for the backward transition from moderate AD to mild AD (albeit with wide confidence intervals for both arms), and that there may be a divergence towards the end of the trial period for the backward transition from mild AD to MCI due to AD. In addition, hazard rates for transition 2 (mild AD to moderate AD) were almost identical between treatments at the end of the trial period, suggesting a decrease in the treatment effect over time. Numbers of patients were not provided at this point, and confidence intervals are wide, hence there may be considerable uncertainty about this observation.

Based on fit to the observed data (both visual and statistical), the Weibull distribution was selected for transitions 1-3 while the Exponential distribution was selected for transition 4. The EAG considers the company's model choices broadly appropriate but also notes that the company still over-estimates state membership for more severe states and death compared with Clarity AD and the IPECAD models. This may warrant exploration of alternative transition probabilities that result in health state membership more in line with Clarity AD. For example, the EAG might have considered the lognormal as a suitable candidate as well as it had the best statistical fit for transitions 1 and 3, but acknowledged that the lognormal distribution exhibited a decreasing hazard pattern over time, which was inconsistent with the smoothed hazard plots that suggested increasing hazards over the duration of Clarity AD. However, the EAG would prefer survival models that result in health state occupancy in line with Clarity AD over accurately representing the hazard pattern over time and considers that alternative distributions should be explored.

2.1.2.1.2 Scenario analyses including the OLE phase of Clarity AD

A scenario was explored using data from the OLE phase of Clarity AD (for the first 36 months in the model), i.e. patients randomised to lecanemab in the core study who continued in the OLE phase. The multistate survival models were fit independently (relaxing the proportional hazards assumption). In this scenario, multistate survival models from the company's base-case were used for the first 18 months. For 18-36 months, lecanemab transition probabilities were informed by the Clarity AD OLE multistate model and the treatment effect for lecanemab vs. placebo from the associated Clarity AD core study analysis (0-18 month) multistate model was applied to the lecanemab transition probabilities to estimate the SoC transitions. Beyond month 36, SoC transitions were informed by natural history data and lecanemab transitions were informed by applying the time-to-worsening hazard ratios, as per the base case.

The EAG appreciates that the company makes use of all available data and agrees that this may be an informative scenario analysis. On the other hand, the EAG was unsure whether the OLE data may exhibit selection bias, e.g. if only people that had not discontinued were in this OLE study; and how this would affect the validity of the model that starts out with the ITT analysis informing the first 18 months. The EAG notes that the relative treatment effect in this scenario was still informed by the 0-18 months data, mitigating this potential bias but also resulting in limited additional information. The EAG also notes the relatively small impact of all configurations of this scenario on the ICER.

2.1.2.1.3 Scenario analyses including alternative mortality assumptions

Noting that the model estimated higher mortality than Clarity AD, the company explored different mortality scenarios from the original CS to consider if any were better aligned with Clarity AD and reverted to using the hazard ratio by Crowell et al for the MCI due to AD health state in its base-case, rather than assuming mortality in the MCI due to AD health state equal to that in the general population. The EAG agrees with the company that this results in greater alignment of modelled mortality with that observed in the trial, but it refers back to its original critique and Crowell et al's[7] statement that relative

mortality for the MCI due to AD health state compared with cognitively normal participants may have been underestimated, due to the more restrictive eligibility criteria for including people in the AD cohort compared with the cognitively normal arm of their study. Thus, the EAG continues to use general population mortality in its base-case.

2.1.2.1.4 Validation of transition probabilities versus Clarity AD and IPECAD models

According to the ACD (3.13) "*The committee noted that it had not been presented with enough information to have confidence in the face validity of the transition probabilities in the model. It noted that the multistate survival approach may provide results with better face validity, and would like to see this explored further. The committee concluded that it would like to see transition probabilities used that lead to outcomes and mortality benefit consistent with trial data and clinical expectations. To verify this, it concluded that it would like to see disaggregated, discounted and undiscounted results for the company's and EAG's base cases, by modelled health states. It would also like to see scenario analyses in which the model structure is revised so that each node only has 2 model transitions, to align with the first solution proposed by Gidwani et al.*"

As requested by the committee, the company provided comparisons to show that outcomes and mortality benefit resulting from the company's model are consistent with the trial and clinical expectations. To enable this comparison and validate the modelling approach, the health state occupancy graphs were produced by the company using the baseline proportions of MCI due to AD and mild AD patients from Clarity AD, as defined by CDR-SB (78.6% MCI due to AD, 21.4% mild AD).

In Tables 52-54 and Figures 45-46 of the response to DG appendices, a comparison with the company base-case and Clarity AD was made with regards to health state occupancy over time.[2] The differences between the company base-case and Clarity AD differed between the health states. The economic model generally underestimates the health state occupancy for the mild health sates (i.e. MCI due to AD and Mild AD) while health state occupancy is overestimated for the more severe health state (i.e. Moderate AD and Severe AD) and death (See Table 54 of the response to DG appendices).[2] This is likely to induce bias favouring lecanemab as this over and underestimation seems to be more prominent for SoC (see "Lecanemab vs. SoC" in Table 54).[2] Therefore, based on the current assessment, the EAG considers that the company's economic model does not accurately predict the state occupancy as observed in Clarity AD for both treatments and that there is a potential bias favouring the effectiveness of lecanemab. Additionally, the scenario mentioned above by the committee was not provided by the company.

Also, when compared with the IPECAD models (original CS Tables 71-72[4] and clarification response Tables 74-77),[10] the duration of health state occupancy in the Severe AD health state (as well as the combined moderate/severe AD health states) is substantially overestimated, and ideally the company would provide per year health state occupancy comparisons of their model estimates with those estimated by other models.[11]

It remains unclear what exactly causes the observed discrepancy between modelled and observed health state occupancy. Ideally the company should provide further information to resolve this issue to support the credibility of the results. Potential causes, according to the EAG might be related to the external evidence used to inform the transition probabilities (specifically to the severe health state which are sourced from Potashman et al.[9]), or the approach to estimate the transition probabilities (i.e. whether this can be resolved by alternative survival models used or the Gidwani et al.[8] scenario that was requested by the committee but not provided by the company).

2.1.2.2 Stopping rules (Comment 7)

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

2.1.2.2.1 Severity-based stopping rule

To address the committee's request for more information from the company on how the stopping rule would be applied in practice, the company consulted three clinical experts and NHS England. Based on these responses the company considered the severity-based stopping rule to be feasible and practical.

The EAG notes that there continues to be a lack of clarity on the way this could be implemented in UK clinical practice. One expert stated that they did not expect differences in staging practices for lecanemab patients compared to those receiving existing standard of care treatments but stated that this "may change with the availability of blood biomarkers to monitor progression". The EAG is unsure about the implications of this, as one interpretation could be that a severity-based stopping rule would not be facilitated under these conditions, as it understands that currently no regular staging (using CDR-SB) is undertaken. The company did not provide further context on this response. The two other experts considered that staging could be conducted concurrently with lecanemab infusion visits using straightforward cognitive tests, such as the Montreal Cognitive Assessment (MoCA). In addition, NHS England's response led the company to implement a scenario in which patients have quarterly outpatient appointments whilst receiving lecanemab to reflect the expected resource requirements of implementing the moderate AD stopping rule in practice.

The EAG accepts that a solution can potentially be found for the implementation of a severity-based stopping rule and considers that when such a stopping rule is modelled that the resource use and costs needed should also be incorporated in the modelling (in line with the committee's request for clarification that the resource impact of implementing this stopping rule in the NHS had been adequately included in the modelling, for example, through sufficient follow-up appointments on lecanemab to assess disease progression). The EAG therefore uses the severity-based stopping rule and adopts the company's scenario costing quarterly outpatient appointments whilst receiving lecanemab in its base-case.

2.1.2.2.2 Institutionalisation-based stopping rule

In the draft guidance, the committee concluded that it was not appropriate to apply a stopping rule based on entry to residential care. The company in their response reiterate expert opinion from their advisory board that indicated that continuing lecanemab in the residential care setting would not be appropriate and also consulted with additional clinical experts. Broadly, these thought that discussion of discontinuation would be reasonable for patients who have entered residential care because of their disease. For respite care, continuation with lecanemab was considered appropriate and the company clarified that in their model the rate of institutionalisation used did not include patients admitted for respite care.

The EAG notes that in the model patients with mild AD can be institutionalised, according to the source Knapp et al.[12] When a severity-based stopping rule is in place that entails treatment discontinuation upon progression to moderate disease, the question is thus whether these patients with mild AD that get institutionalised should discontinue lecanemab. The company did not present reasons for why patients with mild AD move into residential care in the model, especially given that patients admitted for respite care were excluded. The EAG therefore finds it difficult to conclude that treatment discontinuation for

patients with mild AD moving to residential care is the default position, especially considering that the company *"believe this does not translate to a stopping rule in which all patients who enter institutional care must discontinue"* and disables this setting in the EAG base-case.

2.1.2.3 Treatment effect waning and treatment discontinuation (Comment 8)

2.1.2.3.1 Treatment effect waning

In the draft guidance the committee concluded that it was inappropriate to assume that people who stopped treatment in the MCI and mild dementia caused by Alzheimer's disease health states continued to have the same treatment benefits as people who remained on treatment and it concluded that it would like to see alternative treatment-effect waning scenarios, as well as scenarios varying the all-cause discontinuation rate after 18 months.

The company consulted two experts who indicated they would expect to see a continued effect while plaque levels remained low, 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. The EAG notes that the expert opinion appears to be based on two assumptions: that the treatment effect entirely operates through reduction in amyloid, and that amyloid will re-accumulate at a rate that keeps it lower than what it would have been without lecanemab treatment. In the absence of evidence on both of these assumptions, the EAG considers that it is plausible that the treatment effect will diminish because the amyloid level might catch up and / or the treatment effect / disease pathogenesis does not operate entirely through this mechanism. Hence, the EAG agrees with the committee that treatment effect waning scenarios should be explored.

The company maintained that treatment effect waning [redacted] would be inappropriate. It justified this based on precedent from NICE appraisals in AD to assume no treatment effect waning following discontinuation, the clinical plausibility for a maintained treatment effect, and the conclusions in a review of treatment effect waning in NICE technology appraisals.[13] The EAG notes that Trigg et al. cautions against overreliance on previous NICE technology appraisals, that treatment effect waning assumptions (as opposed to immediate loss of treatment effect) would allow a maintained treatment effect (albeit at a lower level than the full treatment effect), and that exploring treatment effect waning does not contradict the conclusions made by Trigg et al.[13] In addition, the EAG notes that while reasons for discontinuation in the trial did not include inadequate therapeutic effect, this does not mean that these patients have not lost response to treatment as indicated by the company or would not have lost response soon after discontinuation. Therefore, the EAG did not see a convincing argument for assuming the full treatment effect for all patients that discontinue lecanemab treatment in the MCI due to AD and mild AD health states for the entire model time horizon.

The company did provide a scenario in which [redacted].

The EAG considers that this does not fully explore the uncertainty and could be considered optimistic for lecanemab, first, because treatment effect waning [redacted]

[redacted]. Second, the [redacted] after treatment discontinuation is arbitrary and could be considered late, also considering that commonly this is applied since the start and not upon treatment discontinuation. The EAG would have liked to see different time points from randomisation to be explored. Third, the choice of applying treatment effect waning [redacted] is also arbitrary as acknowledged by the company. Fourth, the EAG was unsure about the implementation as the company implemented waning by estimating the proportion of patients eligible for waning at each cycle, which was calculated based on the time spent in the health state. The EAG thinks that it might be possible in the model for patients to discontinue treatment in the MCI due to AD state and move to the mild AD state before treatment effect waning is started in the MCI due to AD state, thereby artificially delaying the onset of treatment effect waning in the model. The EAG acknowledges the challenges in modelling this without the use of tunnel states and proposes the simplification of starting treatment waning from a time point after the median time to treatment discontinuation (implemented from the start of the model) on 50% of the patients.

Unfortunately, there is no information on the amount of treatment effect waning that can be expected after lecanemab discontinuation. The EAG considered that the plausible range is between no treatment effect waning and immediate treatment effect stop. Because of the abovementioned concerns, the EAG does not use the company's treatment effect waning scenario but instead sets the expected treatment effect in the off-treatment MCI due to AD and mild AD health states (also for residential care) to 75%.

2.1.2.3.2 All-cause discontinuation

Because the committee also noted uncertainty surrounding the all-cause discontinuation rate after 18 months, the company presented a scenario in which the all-cause discontinuation rate after 18-months was based on 36-month data from the Clarity AD open label extension study, as per the committee's request. The EAG assumes that this is based on more mature data than the original estimate and adopts this scenario in its base-case.

2.1.3 Health-related quality of life (Comment 9)

2.1.3.1 MMRM utility model

In the draft guidance, "*the committee concluded that it would like to see a detailed outline of the utility values used for each health state, the data source for them and justification for that source. It would also like to see a complete EAG critique of the final approach*." As highlighted in 1.1.4 EAG comment, while the company provide detail regarding the updated MMRM approach to estimating utilities, details to assess the implementation of the approach are outstanding. Specifically, to validate the approach, the EAG would like to see the following additional evidence/analyses:

- MMRM backward elimination process: utilise α=0.05
- Patient-reported EQ-5D utilities to inform MCI due to AD and Mild AD HSUVs
- For validation:
    - linearity of relationships between the predictors and the outcome variable,
    - normality of the errors, homogeneity of error variance (homoscedasticity),
    - independence, i.e. effects associated with the random variable groups are uncorrelated with the means of the fixed effect from the random variable groups
    - model specification – the model should be properly specified (including all relevant variables, and excluding irrelevant variables)
    - examining individual observations that exert undue influence on the coefficients multicollinearity.

- Further explanation as to how utility values are calculated in the model (e.g., whether Geographical Region – Europe covariate is included in the utility estimates)
- Justification for observed utility discrepancies (Table 11 submission addendum vs Table 42 DG appendices)
- Missing data imputation
    - Justification for assuming missing data is missing at random, or, if not; consi
    - Performing missing data imputation

As stated in section 1.1.4, the EAG would prefer the use of patient-reported EQ-5D for MCI due to AD and Mild AD health states, recognising the counter-intuitive results and the minimal impact on the ICER. In addition, the EAG recommends removing the fixed effects covariate for treatment.

2.1.3.2 Carer QoL

The company revisited the approach taken to estimate carer utilities. The CS explored two approaches: a decrement approach (CS base-case), and an additive approach (CS scenario analysis). The company highlight disadvantages to both approaches: the decrement approach results in the caregiver QALY trap (i.e., a patient dying implies caregiver quality of life improves); the additive approach assumes no value is placed on the bereaved carer (implicitly assumed that the carer either dies or survives with zero utility). As such, the company now utilise a utility increment approach. Here, severe AD (institutional setting) is the reference (utility: [redacted]) with utility increments calculated relative to this health state for all other health states. Utility increments for each health state are presented in DG appendices Table 43. The EAG recognise the potential importance of the caregiver QALY trap (see Mott et al., 2023[14]). With reference to EAG comment c) of 4.2.8 (Health-related quality of life) in the EAG report,[6] the EAG notes the uncertainty associated with calculating caregiver utility increments using severe AD in the institutional setting as a reference point. That is, the EAG highlight the lack of evidence to suggest any difference between caregiver utility between care settings for each health state. The EAG thus disabled this utility decrement in its base-case. This was not adopted in the updated company base-case. Indeed, the increment approach adopted by the company in the updated submission reduced the ICER by [redacted]. As such, if a caregiver utility decrement, when going from a community setting to institutional setting, is not plausible, the caregiver QALYs applied to institutional settings likely underestimate institutional utility. This comment was not addressed in the updated submission. The EAG re-adopted the removal of a utility decrement from community to institutionalised settings and maintained the company's increment approach in its base case. As such, the caregiver utility increments are equal for each health state between the community and institutional setting.

2.1.4 Resource use and costs

2.1.4.1 Infusion costs (Comment 10)

To address the committee's request for further information regarding the estimated cost of lecanemab infusion, including a breakdown of expected resource use and exploration of alternatives, the company conducted the following activities:

- Sought additional clinical expert opinion on the appropriate infusion cost for lecanemab
- Conducted a hand search of administration costs used for other monoclonal antibodies in previous NICE technology appraisals (TAs)
- Conducted a micro-costing study on the healthcare professional time taken for tasks related to administration of lecanemab.

The company stated that two of the three clinicians agreed that chemotherapy was an appropriate proxy, whilst none believed that WD02Z was appropriate. The EAG, however, could not find these statements in the document the company referred to[15] and was therefore unable to verify this.

The review of NICE TAs of monoclonal antibodies administered via IV infusion published over the last six years (2018-2024) identified TA897, TA585, TA862, TA540, TA763, and TA798. HRG code SB12Z was used in three appraisals (TA798, TA862, and TA540). Two appraisals (TA763 and TA897) had varying infusion times for initial and subsequent infusions, which were substantially longer than the lecanemab infusion time. The infusion costs of the remaining multiple sclerosis appraisal (TA585) was also considered an inappropriate proxy by the company as blood drawing prior to treatment was required, which is not required for lecanemab. The EAG noted that both the company's initially modelled infusion cost (£208) and updated infusion cost ([redacted]) are lower than the infusion costs reported in the identified TAs.

To address the committee's request for a breakdown of resource use for the administration of lecanemab, the company conducted a micro-costing exercise to estimate the time and staff resource needed to administer lecanemab in NHS practice based on a study by Burcombe et al. (2013).[16] The infusion cost estimated by the micro-costing is [redacted], which is lower than SB12Z and substantially lower than WD02Z. The company stated that this implies that SB12Z is a conservative estimate of the cost of administering lecanemab and adopted the micro-costing estimate in its base-case.

The EAG is unsure whether the Burcombe et al.[16] study is suitable for the approximation of lecanameb infusion costs. In addition, the EAG noted that there was substantial variability between the HCP inputs within the company's micro-costing exercise. The EAG also took note of the NHSE response, which states that the chemotherapy tariff is not appropriate because lecanemab requires more complex preparation prior to its administration and carries a higher risk of adverse infusion reaction which will impact on treatment monitoring and staffing requirements. The cohort of patients potentially eligible for lecanemab will be older, and may also have more complex needs, on average, than those receiving chemotherapy. The NHSE response also provided further justification for their choice of ICD10 code X292, which they think is how most health care provider would code the activity.

NHSE also provided a new alternative pricing approach to the administration of lecanemab, which is consistent with the pricing assumed within the NICE appraisal process for monoclonal antibodies (MABs) administered in the management of a confirmed COVID infection. This pricing was supported by bottom-up costing work undertaken on the basis of actual NHS use of monoclonal antibodies administered by infusion, by a sub-set of COVID Medicine Delivery Units. This approach results in an administration cost of £432. NHSE notes that this approach would require a minor update to the annual coding guidance provided to NHS providers, and for providers to specifically record the administration of lecanemab in Secondary Uses Services.

The newly proposed NHSE cost estimate is used in the EAG base-case.[17]

2.1.4.2 Private care costs (Comment 11)

"The committee concluded that it was unclear what proportion of the costs used by the company could be attributed to private costs and so excluded. It noted that it would like to see further justification for the appropriate proportion of the costs assumed be for private care."[3]

The company sought clarification from the authors of the Alzheimer's Society UK report on the proportion of costs that are private, but did not get a response.

Alternatively, the company used the estimate from an Alzheimer's Society blog of 63% of all dementia costs being borne privately to estimate the proportion of non-medical costs borne privately. The company stated that the total dementia costs reported in the Alzheimer's Society Dementia UK update, inclusive of medical, non-medical, unpaid care, and other costs, is £26,316. Then, the proportion of this borne privately (63%, based on the Alzheimer's Society blog) was calculated (£16,579.39) and other private care costs were subtracted from this. This resulted in a total of £4,848 representing non-medical costs borne privately, equating to 47.2% (=4,848/10,271). The company included a scenario analysis in their updated economic model in which non-medical health state costs are reduced by 47.2%. The EAG agrees on the company's approach, but considers that it should be in their base-case. The EAG therefore adopted the company's approach of reducing non-medical health state costs by 47.2% in the EAG base-case.

2.1.4.3 Amyloid beta testing costs

"The committee concluded that it was appropriate for the company to assume that 90% of people tested for amyloid beta will have a lumbar puncture and 10% will have a PET-CT scan. It also concluded that it was appropriate to assume that 28.8% of people who are tested for amyloid beta will not have amyloid pathology, so will not be eligible for lecanemab."[3]

The company implemented this and the EAG has no further comment.

2.2 EAG analyses

2.2.1 EAG base-case

As per the critique points above, the EAG made the following changes to the company's post ACM1 base-case (Table 6):

1. Treatment effect waning: 75% treatment effect immediately upon discontinuation for MCI due to AD and mild AD states (community and residential care)
2. All-cause discontinuation: updated rates based on OLE study
3. Disable institution-based stopping rule
4. Mortality in MCI due to AD = general population
5. Disable caregiver institutionalisation disutility
6. Include quarterly outpatient costs to support the severity-based stopping rule
7. Infusion costs as per NHSE updated pricing
8. Exclusion of private care costs from non-medical health state costs (47.2% reduction)
9. MMRM utilities: Removal of treatment fixed effects covariate and use of patient reported values
10. Disable treatment effect in mild AD to severe AD transition

2.2.2 EAG scenarios

Given the uncertainty around treatment effect waning, administration costs and estimated transition probabilities, the EAG explored the following scenarios (Table 7):

1. Instant & complete treatment effect waning: 0% tx effect immediately upon discontinuation for MCI and mild AD states (community and residential care)
2. No treatment effect waning: 100% tx effect upon discontinuation for MCI and mild AD states (community and residential care)
3. Use of HRG code SB12Z for infusion costs

4. Lognormal distribution for multistate transitions 1-3

2.2.3 Subgroup analysis

No subgroup analysis was provided by the company.

2.2.4 Cost-effectiveness results

Table 6: EAG amendments to post ACM1 company base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Treatment effect waning: 75% tx effect immediately upon discontinuation for MCI and mild AD states (community and residential care)							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. All-cause discontinuation: updated rates based on OLE study							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Disable institution-based stopping rule							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Mortality in MCI due to AD = general population							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Disable caregiver institutionalisation disutility							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Include quarterly outpatient costs							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Infusion costs as per NHSE updated pricing							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8. Exclusion of private care costs from non-medical health state costs (47.2% reduction)							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. MMRM utilities: removal of treatment fixed effects covariate and use of patient reported values							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Disable treatment effect in mild AD to severe AD transition							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG post ACM1 base-case							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[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 an error in the macro and overwriting of EAG changes with default values).							

Table 7: EAG scenarios conditional on EAG post ACM1 base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG post ACM1 base-case							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1. Instant & complete treatment effect waning: 0% tx effect immediately upon discontinuation for MCI and mild AD states (community and residential care)							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S2. No treatment effect waning: 100% tx effect upon discontinuation for MCI and mild AD states (community and residential care)							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3. Use of HRG code SB12Z for infusion costs							

Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4. Lognormal distribution for transitions 1-3							
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[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							

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

Updated Managed Access Proposal

Introduction

Eisai is the marketing authorisation holder of lecanemab (LEQEMBI®), an amyloid beta (Aβ)-directed antibody indicated for early Alzheimer's disease in countries including the US, Japan and China.[1-3]

Lecanemab was granted an Innovation Passport under the Innovative Licensing and Access Pathway (ILAP)[4] in February 2023 and marketing authorisation by the MHRA on 22 August 2024 in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers.[5] This was based on data from an 18-month Phase 3 trial, Clarity AD (van Dyck et al., 2022, NEJM), in which the primary and all key secondary endpoints met with highly significant results.[6]

Alzheimer's disease (AD) is an irreversible neurodegenerative disease that causes progressive cognitive and functional decline.[7] It is the leading cause of cognitive impairment in individuals aged ≥65 worldwide and is the most common form of dementia.[8,9] The NICE guideline for the assessment and management of dementia (NG97) provides a clinical care pathway for AD, which includes procedures for assessment and diagnosis, catering to both non-specialist and specialist healthcare settings.[10] However, no treatment guidelines exist for MCI due to AD. Available treatments for AD in the UK clinical pathway provide only symptomatic relief but do not treat the underlying cause of AD nor delay the progression of the disease, highlighting the unmet need for effective disease modifying therapies (DMTs) in AD. Please see section B.1.3.6 of the ID4043 company evidence submission for further details.[11]

[redacted]

[redacted]

[redacted]

Potential data sources

The pivotal phase 3 Clarity AD trial is comprised of an 18-month core study of lecanemab vs placebo in patients with early AD, followed by a single-arm open-label extension (OLE) study where all patients may receive lecanemab if they meet the OLE inclusion criteria. The Clarity AD core study is complete and informed the ID4043 company evidence submission.

The Clarity AD OLE is ongoing, during which patients may continue to receive open-label lecanemab 10 mg/kg every two weeks via IV infusions as per the core study, or a subcutaneous formulation if they entered one of the associated substudies. Patients receiving lecanemab IV 10 mg/kg every two weeks will continue for up to a maximum of 4 years in the clinic, until the drug is commercially available in the country where the patient resides (after which sites can transition patients out of the OLE study onto commercial supply), or until the benefit-to-risk assessment from treatment with lecanemab is no longer considered favourable, whichever comes first.

It is therefore not possible to predict the numbers at risk at future data cuts, however the following data from the OLE are currently available, [redacted]:

- Interim efficacy results based on a data cut-off of 13 March 2023, which provides **6 months of follow-up** (24 months including the Clarity AD core study follow-up) were presented at the Clinical Trials on Alzheimer's Disease conference meeting in October 2023, as detailed in our response to ID4043 clarification question A14.[12] At this data cutoff, [redacted] **patients** who received lecanemab IV bi-weekly in the core study and continued to receive this regimen.
- **18-month follow-up** (36 months including the Clarity AD core study follow-up) was presented at the Alzheimer's Association International Conference (AAIC) in July 2024. At this data cutoff, data were available for [redacted] **patients** in the indicated population who received lecanemab IV bi-weekly in the core study and continued to receive this regimen.

Therefore, the Clarity AD OLE is a relevant source of long-term data (up to 4 years follow-up additional to 18 months from the core study) for lecanemab IV 10 mg/kg biweekly for endpoints informing the cost-effectiveness analysis and is expected to provide follow-up beyond the current appraisal and guidance publication.

The NICE managed access feasibility assessment cited the OLE data are confounded by treatment switching. This is incorrect as the patients who switch from placebo to lecanemab are analysed separately (termed ‘delayed-start group’) from those who were randomised to lecanemab in the core study (termed ‘early-start group’).

Equivalent follow-up from the Clarity AD placebo arm will not be available beyond 18 months because these patients switch to receive lecanemab in the OLE study. However, the OLE data presented to-date have been compared with an observational cohort of

participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database who were matched with the Clarity AD population based on baseline demographics and clinical characteristics, including randomisation strata.

NHS infrastructure and collection of AD-related data

Presently, Eisai is not aware of infrastructure or registries in England for collecting data from AD patients treated in NHS practice. [redacted]

Key uncertainties identified in draft guidance

The key uncertainties identified in the draft guidance and how Eisai believe these can be addressed during managed access are summarised in the table below. Eisai deems the following key uncertainties in the draft guidance to be methodological and/or believes these have been addressed (i.e. demonstrated to not translate into cost-effectiveness uncertainty) in the company draft guidance response and are therefore not included in the updated managed access proposal:

- Face validity of transition probabilities
- Impact of treatment discontinuation on outcomes
- Utility values used in the model
- Diagnostic and private care costs

Table 1. Summary of key uncertainties in draft guidance

Key uncertainty	Is this expected to be addressed by company draft guidance response?	Could this be addressed by managed access?
Administration cost	[redacted]	[redacted]
AD progression (long term trends)	[redacted]	[redacted]
Proportion MCI vs. mild AD	[redacted]	[redacted]
Treatment discontinuation	[redacted]	[redacted]
Stopping rule for moderate AD	[redacted]	[redacted]
Stopping rule for institutional care	[redacted]	[redacted]

Data Collection Proposal

The updated company data collection proposal is outlined in Table 2. The duration of the data collection period could be linked with completion of the Clarity AD OLE study (a maximum 4 years) expected mid-2027, as this would enable the maximum follow-up from this study to inform NICE reappraisal.

[redacted]

[redacted]

Table 2. Updated Data Collection Proposal

Clinical uncertainty	Data required for NICE reappraisal	Potential data sources	Duration of data collection	How does this address NICE MAT feasibility assessment
Clinical effectiveness (disease progression)	[redacted]	Clarity AD OLE study will provide longer follow-up for lecanemab, but not standard of care.	Clarity AD OLE will run for up to a maximum 4 years	[redacted]
Lecanemab compliance	[redacted]	Clarity AD OLE	As per clinical effectiveness	
		NHS practice	TBC	[redacted]
Discontinuation rate /time-on-treatment	[redacted]	Clarity AD OLE	As per clinical effectiveness	[redacted]
		NHS practice	TBC	
Baseline patient characteristics	[redacted]	Clarity AD OLE	Already available	
		NHS practice	Baseline for all patients treated during data collection period	
Lecanemab intravenous administration cost	[redacted]	[redacted]	TBC	[redacted]

Abbreviations: CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating–Sum of Boxes; NHS – National Health Service; OLE – open-label extension

Anticipated patient numbers in NHS England

The eligible population for lecanemab is people with MCI due to AD or mild dementia due to AD that are ApoE ε4 heterozygotes or non-carriers. Patients must also have confirmed amyloid beta (Aβ) pathology.

As described in the ID4043 company budget impact submission, the prevalent eligible patient population in Year 1 (based on population estimates in England in 2024) is estimated to be 44,270, of which 22,932 have MCI due to AD and 21,338 have mild dementia due to AD (Table 2).[13] This will now be reduced by 15% to reflect the marketing authorisation which excludes patients that are ApoE ε4 homozygotes. Further details regarding estimation of the eligible and treatable population can be found in the ID4043 company budget impact submission.

Currently, dementia services in NHS England are not set up to diagnose, infuse and monitor all early AD patients with Aβ pathology with a therapy such as lecanemab, due to limitations in required AD specialist resources, infrastructure and equipment.[14] Consequently, the treatable population is expected to represent a small proportion of the eligible population in the initial years following the introduction of lecanemab. [redacted].

After accounting for NHS capacity constraints, the incident treatable population in Year 1 is estimated to be [redacted] patients, of which [redacted] have MCI due to AD and [redacted] have mild dementia due to AD. This increases to [redacted] in year 3. The number of patients expected to start treatment with lecanemab in year 1 is [redacted], increasing to [redacted] in year 3 (Table 2). The extent to which these numbers reflect clinical practice will depend on [redacted] and the evolution of the NHS service over this time period.

Table 2: Eligible and treatable population estimates

Population	Year 1*	Year 2	Year 3	Year 4	Year 5
Prevalent early AD	44,270	44,972	45,691	46,532	47,331
Prevalent eligible early AD (i.e. APOE4 non-carrier or heterozygote)	37,497	38,091	38,700	39,413	40,089
MCI due to AD	19,423	19,696	19,953	20,292	20,584
Mild dementia due to AD	18,073	18,395	18,747	19,121	19,506
NHS capacity adjustment	2%	4%	8%	16%	32%
Prevalent treatable early AD	750	1,524	3,096	6,306	12,829
MCI due to AD	388	788	1,596	3,247	6,587
Mild dementia due to AD	361	736	1,500	3,059	6,242
Incident treatable early AD	750	774	1,572	3,210	6,523
MCI due to AD	388	399	808	1,650	3,340
Mild dementia due to AD	361	374	764	1,560	3,183
Population expected to start treatment with lecanemab (incident)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; MCI – Mild cognitive impairment; NHS – National Health Service
*Assumed to be 2024

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Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease**

Topic ID: **4043**
Managed Access Lead: **Steve Norton**
Date of assessment(s): **21/03/2024**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	There is limited data collection that can be achieved through the clinical trial and it is unclear for how long it will be continuing. RWE is not being collected for this population. Setting up a de novo RWE data collection would likely require significant time and resources to set-up. If it were to be set-up, data collection within managed access would cause some burden on patients and the system. Giving access to only a portion of the eligible population is against the principles of the IMF and managed access as a whole.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Unclear	There is a clear unmet need in a priority area but current data collection plans would not resolve uncertainties.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	No	Consider this rating to be non-binding. Most early uncertainties identified can be resolved with committee decision making. Some uncertainties may feasibly benefit from data collection in the IMF. In practice, a useful data set may be difficult to obtain. Since data is unlikely to be forthcoming from NHS sources, this will depend on the company's data gathering.
Can data collection be completed without undue burden on patients or the NHS system	No	High burden on patients and the system as no RWE data collection is currently in place. This would be made more complex by needing to coordinate across primary and secondary care. A large indication with significant deviations from current practice risks high strain on the system.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	Yes - Minor	Implementation will need a large change to service provision and would need significant resources to roll out. Any restricted implementation (unless due to service capacity constraints) would go against the IMF principles.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered	
1	Which uncertainties should be addressed in managed access – does managed access need the full proposal to be implemented to have value? Which items are essential even if data collection does not currently exist and may be complex? Can managed access be useful even if some aspects of the proposal are not implemented?
2	For which uncertainties above would NHSE data collection be essential?
3	Which baseline characteristics should be collected (CDR-SB, subgroup status, EQ-5D-5L...)?
4	Is the company's proposal is adequate to generate appropriate data?
5	Would implementing any of the proposed data collections would result in undue burden on the NHS, clinicians or patients?

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	16/10/2024

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Unclear	Alzheimer's and dementia are priority areas for the NHS and there is a high unmet need. However, limited data collection means the value of placing this topic into managed access is minimal.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	People with mild cognitive impairment and mild dementia caused by Alzheimer's disease have a high unmet need because treatment options are limited and ineffective.
Potential to provide significant clinical benefits to patients	Rate of cognitive decline is significantly slower for people on lecanemab vs placebo. It is difficult to ascertain the clinical significance of the rate change but it is reasonable to say a modest slowing of dementia would have significant clinical benefits to this population. It is important to note the safety profile of lecanemab and whether it is reasonable.
represents a step-change in medicine for patients and clinicians	People in this indication currently have no or limited treatment options, such as AChE inhibitor.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	Current avenues for data collection are limited.

System implementation	Supporting Evidence
The technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning	This treatment is being considered as a candidate for a number of potential routes to commissioning.

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Medium	The uncertainties listed have been extensively updated following NICE's Draft Gudiance (MAT and EAG uncertainties are no longer considered the official list of uncertainties but are preserved here for information only, hence they are greyed-out). We ahve engaged with NHSE and ht ecompany to understand the latest proposal to address these uncertainties through managed access data collection, and we believe some uncertainties stand a reasonable chance of being somewhat resovled through data collection in the ongoing trial and in clinical practice. Implementation of data colleciton in clinical practice may be impractical, reducing the feasibility of the proposal resolving the uncertainties.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
MAT1	Long term efficacy	There is comparative data for the first 18 months. The study has become a longer term open label extension study where people on placebo can switch to treatment.	NA	Unquantified	Longer term data	Clarity AD OLE study	Medium	Unclear whether OLE period will extend beyond appraisal and guidance publication. OLE data will not be comparative and confounded with treatment switching meaning limited inferences can be drawn from them.
MAT2	Patient health-related quality of life in more severe stages	Company suggests they will use proxy reported utilities in more severe stages of the disease as in TA217 because accurate QoL reporting in this population is difficult.	NA	Unquantified	NA	NA	No further data collection possible / proposed	No ongoing data collection is currently available to resolve this uncertainty. Data collection is theoretically possible but there would have to be good rationale to set-up de novo data collection since there a dataset already exists.
MAT3	Caregiver quality of life	The company note the counterintuitive impact of reducing time spent institutionalised by the patient by increasing burden on the caregiver. They wish to explore different assumptions and inputs relating to caregiver quality of life.	NA	Unquantified	Data on caregiver quality of life	NA	No further data collection possible / proposed	Committee judgement needed. No ongoing data collection is currently available to resolve this uncertainty.
MAT4	Modelling disease progression	The company have suggested using natural history data from various databases (see decision problem form for detail) but none are UK-specific. The company have ruled out a UK-based study because of the small sample size, inclusion of vascular dementia patients and uncertainty in amyloid status.	NA	Unquantified	NA	NA	No further data collection possible / proposed	Committee judgement needed.

EAG1	Need to test for Aβ disease to establish population eligible for lecanemab	The population in the key clinical trial, Clarity AD, and of those eligible for lecanemab is narrower than that specified in the NICE final scope (although the economic analysis section of the scope does state "the use of lecanemab is conditional on the presence of amyloid pathology"), being defined by the presence of Aβ pathology, which requires one of the following: •CSF biomarker test •Amyloid PET scan	Incorporating cost of testing	Medium	Evidence as to the harm of any testing and its incorporation into the cost effectiveness analysis.	Further analysis	No further data collection possible / proposed	
EAG2	Appropriateness of the SoC comparator for the MCI due to AD population	The CS does not include any data about the comparative effects of lecanemab vs. non-pharmacological management (as specified in the NICE scope). This is because the key study (Clarity AD) was conducted in a mixed population (MCI due to AD and mild dementia due to AD) and over half of the patients in the study were receiving other pharmacological interventions for AD (AChEis and/or memantine).	Provision of subgroup analyses for participants with MCI due to AD, who did not receive symptomatic AD medication (AChEi or memantine) during the study (Clarity AD). These analyses were requested at clarification and have been provided.	Medium	The EAG considers that there is currently no further clinical effectiveness evidence available that could resolve this uncertainty. However, a cost effectiveness analysis for this subgroup still remains to be performed.	Further analysis	No further data collection possible / proposed	
EAG3	Appropriateness of the SoC comparator for the mild dementia due to AD population	The decision problem specifies the comparator, for the mild dementia due to AD population, as AChEi plus non-pharmacological management (amended to AChEi and/or non-pharmacological management in the CS). As with Key issue 1 (see Table 1.2), these comparisons are not directly provided by the reported results of the Clarity AD study. UK clinical guidance (NG97) recommends the use of AChEis, but not memantine, in this population.	Potential undertreatment of the comparator group, for this population, could lead to overestimation of the effects of lecanemab. However, it should be noted that the percentage of patients in the mild subgroup of the Clarity AD trial who received AChEi was not that much less than 70%. Also, the treatment effect increased when patients treated with memantine were excluded.	Unquantified	Provision of subgroup analyses for participants with mild dementia due to AD, excluding: a) those participants who received memantine during the study (consistent with the company's definition of the decision problem); b) those patients who received memantine during the study and those patients who did not receive AChEi during the study (consistent with the NICE final scope). A possible alternative might be confirmation that the proportions of participants with mild dementia due to AD, in both arms of the Clarity AD study, who received treatment with an AChEi or memantine were consistent with UK clinical practice (e.g., 70% and 5% respectively, as indicated by clinical expert opinion. Additional information on the numbers of study participants, with mild dementia due to AD, who received symptomatic AD medication (AChEi or memantine) was provided.	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.	No further data collection possible / proposed	
EAG4	Consideration of relevant clinical subgroups (specified in the NICE scope)	Subgroups specified in the NICE final scope were: apolipoprotein E4 (ApoE4) gene carrier status; MCI due to AD; mild dementia due to AD. Clinical effectiveness subgroup analyses were provided in Appendix E of the CS. Cost effectiveness modelling included scenario analyses considering MCI due to AD mild dementia due to AD populations separately, however, no scenarios based on ApoE4 gene carrier status were presented.		High	Implementation of scenario analysis for ApoE4 gene carrier status, considering non-carrier, heterozygote and homozygote. These analyses were requested and performed by the company at clarification.	Further analysis	No further data collection possible / proposed	
EAG5	Lack of long-term data to support the clinical effectiveness of lecanemab	Clinical effectiveness data, included in the CS, are limited to the results of one RCT (Clarity AD) with a follow-up duration of 18-months.	Given the nature of the condition and of the intervention (lecanemab is a disease-modifying treatment, rather than a treatment of symptoms), 18-months follow-up is unlikely to sufficient to adequately assess treatment effects; for example, any observed initial delay in disease progression may not extrapolate to long-term benefit if the delay in progression does not remain constant and persist beyond 18 months.	Unquantified	Provision of long-term outcome data – there is an OLE to Clarity AD (6 to 48 months), which is ongoing. In its clarification response, the company provided some initial (24-month) results from the OLE. The EAG considers that currently available data are insufficient to adequately demonstrate the long-term efficacy of lecanemab.	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.	High	Longer-term data collection may be established to support resolution of this uncertainty. Unspecified data from clinical practice may be designed to support resolving this uncertainty. The company has also proposed its Clarity AD OLE as a data source, which does not require further implementation to begin collecting data.

EAG6	Uncertain clinical significance of the reported treatment effects	The Clarity AD trial reported that patients treated with lecanemab experienced smaller changes from baseline than those in the placebo group, for all six cognition and function domains of the CDR-SB (the primary outcome measure), however, the absolute difference in change between the treatment and placebo groups was small. Studies cited (references 183 and 186 in the CS) in support of the clinical significance of the treatment effect indicate that an increase of between	Clinical expert opinion (sought by the EAG) regarding what % reduction in decline would be considered clinically meaningful: "This is problematic and likely to be different at different disease stages. Importantly, Individual patients/families will have very different views on what is meaningful for them, depending on their differing values and expectations. When deciding whether to prescribe lecanemab, I would be strongly influenced by	Unquantified	None	Collection of data, ideally long-term (>18 months), on e.g., time to admission to full-time care, time to progression to moderate or severe AD. The EAG considers that there is currently no further evidence available that could resolve this uncertainty.	Medium	It appears somewhat feasible that such evidence could be collected, however this is not currently proposed and would need to be carefully designed.
EAG7	Applicability of the Clarity AD study to the UK setting	The CSR indicates that XX UK patients were included in the Clarity AD study. The CS indicates that approximately XX% of participants in the Clarity AD study had MCI at baseline and approximately XX% had mild AD.	Clinical expert opinion (sought by the EAG) has indicated that; "In the UK, patients are currently more likely to present at the mild dementia than MCI stage, and so the proportions offered lecanemab might be reversed (i.e. XX% MCI, XX% dementia)." Clinical expert opinion (sought by the EAG) has indicated that the proportions of participants in the Clarity AD study (particularly in respect of the population with MCI due to AD) who received concomitant treatment with an AChEi and/or memantine is unlikely to be consistent with current UK clinical practice. Clinical expert opinion (sought by the EAG) has indicated that, whilst CDR-SB is an accepted outcome measure in clinical trials, it is not routinely used on clinical practice	Unquantified	Provision of evidence about the rates of treatment with AChEis and memantine, in the UK, of patients with MCI due to AD and mild dementia due to AD, and/or provision of appropriate subgroup analyses. Both information about the rates of treatment with AChEis and memantine, in the UK, of patients with MCI due to AD and mild dementia due to AD, and subgroup analyses were provided in the clarification response. The EAG considers that the concomitant use of symptomatic AD medication (AChEis and memantine) in the Clarity AD study was unlikely to reflect UK clinical practice, particularly with respect to the management of patients with MCI due to AD. In addition, the EAG considers that the results of the subgroup analyses raise a question about whether lecanemab has a clinically significant effect, in patients with MCI due to AD, when used in the context of UK SoC (i.e., without concomitant symptomatic AD treatment);	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.	Low	It appears arguably feasible that such evidence could be collected, however this is not currently proposed and would need to be carefully designed.
EAG8	Uncertainty about the clinical effects of lecanemab by ApoE4 genotype	Subgroup analyses of data from the Clarity AD study (reported in appendix E of the CS) indicate a substantial variation in treatment effect, for the primary outcome measure (CDR-SB), with ApoE4 genotype: non-carriers (n=542), adjusted mean difference in change from baseline -0.75 (41% slowing of decline); heterozygote (n=924), adjusted mean difference in change from baseline -0.50 (30% slowing of decline); homozygote (n=268), adjusted mean difference in change	Implementation of scenario analysis for ApoE4 gene carrier status, considering non-carrier, heterozygote and homozygote. These analyses were requested at clarification	Unquantified	Collection of more data to inform the possible variation of treatment efficacy by genotype, particularly with respect to the ApoE4 homozygote population.	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.	Low	It appears arguably feasible that such evidence could be collected, however this is not currently proposed and would need to be carefully designed.
EAG9	Uncertainty about the requirements for MRI safety monitoring in relation to ARIA and variation by ApoE4 genotype		The appropriate frequency for MRI safety monitoring is unclear, particularly in relation to additional MRI scans and clinical assessments that may be required, before resumption of treatment, in patients in whom lecanemab treatment has been suspended due to ARIA. There is also some uncertainty around what ARIA-related criteria are recommended to trigger suspension of dosing and what criteria were applied in the Clarity	Unquantified	Provision of more detail about safety monitoring undertaken during the Clarity AD study (Clarification question A23). Provision of data on adverse events of special interest (primarily ARIA) by ApoE4 genotype subgroup.	Further research	No further data collection possible / proposed	
EAG10	Uncertainty about the clinical effects of lecanemab by patient age		Subgroup analyses of data from the Clarity AD study (reported in appendix E of the CS) indicate a possible relationship between treatment effect, for the primary outcome measure (CDR-SB), and patient age: ≥75 years (n=641), adjusted mean difference in change from baseline -0.72 (40% slowing of decline); 65-74 years (n=749), adjusted mean difference in change from baseline -0.37 (23% slowing of decline); <65 years (n=344)	Unquantified	Collection of more data to inform the possible variation of treatment efficacy with patient age.	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.	Low	It appears arguably feasible that such evidence could be collected, however this is not currently proposed and would need to be carefully designed.

EAG11	Starting distribution of patients between MCI due to AD and mild AD in the economic model not in line with UK clinical practice		The proportions of patients who have MCI due to AD or mild AD used in the model are not in line with what is likely seen in UK clinical practice.	Medium	Use proportions in line with EAG clinical expert opinion.	Further analysis	No further data collection possible / proposed	
EAG12	Possible methodological errors in estimation of and questionable validity of transition probabilities	There are three key uncertainties surrounding transition probabilities: •Appropriateness of backward transitions •The use of time-dependent transition probabilities may be more appropriate •Best practices not followed for estimation of transition probabilities under competing risks	•Disable backward transitions in scenario •Perform further validation (such as CS Tables 71-74) on the use of the time-dependent transition probabilities derived using the multistate model; explain how competing risks were handled in the multistate approach •Explore approach 1 detailed in tutorial by Gidwani et al	Medium	The EAG would be interested in how competing risks were handled in the multistate analysis and whether the company consider this analysis more appropriate than the original approach to estimating transition probabilities.	Further analysis	No further data collection possible / proposed	
EAG13	Extrapolation of long-term treatment effect might be implausible	Long-term treatment effect based on assumptions: the hazard ratio estimated from the trial holds throughout model time horizon for patients on treatment (and those discontinued in MCI due to AD and mild AD states)		High	•Explore treatment effect waning scenarios •Off-treatment patients in MCI due to AD/mild AD should have transition probabilities of SoC, not lecanemab	Further analysis	Medium	Unspecified data from clinical practice may be designed to support resolving this uncertainty. The company has also proposed its Clarity AD OLE as a data source, which does not require further implementation to begin collecting data.
EAG14	Mortality estimates in MCI due to AD state in the economic model are implausible	Mortality estimates in the model are below those of the general population for patients with MCI due to AD, which lacks face validity.		High	•Set mortality equal to general population in MCI due to AD health state.	Further analysis	No further data collection possible / proposed	
EAG15	Uncertainty about treatment discontinuation in the economic model	Treatment discontinuation may be over-estimated in the model due to all-cause discontinuation rate assumed constant in trial and beyond; and potential double-counting of all-cause discontinuation and stopping rules. XXXXXX	•Explore no or reduced all-cause treatment discontinuation beyond 18 months. •XXXXX •Disable institutionalisation-based stopping rule in scenario	High	As above. Provide further expert opinion on the appropriateness and operationalisation of stopping rules in practice.	Further analysis	Medium	Unspecified data from clinical practice may be designed to support resolving this uncertainty. The company has also proposed its Clarity AD OLE as a data source, which does not require further implementation to begin collecting data.

EAG16	Methodological uncertainty about approach to estimating utility, and potential face validity issues	Utility values for the MCI due to AD and mild AD health states were calculated as the mean EQ-5D values across all (post-)baseline observations. The approach does not consider within/between-patient variability, ignores potential confounding variables and potentially oversimplifies results through not capturing changes to utility over time. Derived utilities are treatment dependent which cannot be reasonably justified within the current approach. These utility values	The EAG propose an alternative approach (i.e., mixed effects model) to account for potential confounding variables, and to handle variability within and between patients over time. The approach can further be used to assess the plausibility of treatment-dependent utilities. Handling of missing data should be clearly reported and justified. When applying utility decrements, a multiplicative approach should be used.	High	To derive utility values for the MCI due to AD and mild AD health states using an alternative approach (i.e., mixed effects model). When applying utility decrements, a multiplicative approach should be used. Handling of missing data should be clearly reported and justified. The impact of capping or adjusting by general population utility values should be explored	Further analysis	No further data collection possible / proposed	
EAG17	Uncertainty in caregiver disutility due to patient institutionalisation	The CS applied a disutility of 0.09 to capture the impact of patient institutionalisation on caregiver HRQoL. As per consultation with a clinical expert, in addition to the conflicting results from Verbeek et al. with Farina et al1, the impact of institutionalisation on caregiver utilities remains unclear to the EAG.	The EAG disabled the caregiver utility decrement with institutionalisation in its base-case.	High	None	Further analysis	No further data collection possible / proposed	
EAG18	No AE disutilities applied	No AE disutilities were applied in the model, despite HRQoL measures only being administered every six months and AEs of special interest typically being resolved within four months. This is likely to overestimate health state utility values, failing to capture the impact of AEs on HRQoL. Upon request, the company provided a scenario analysis including AE disutilities. However, the scenario seemingly underestimated the duration of AEs, underestimated the disutility for grade 3+ infusion-related	The EAG requested a scenario analysis incorporating AE disutilities, which it has adopted in its base case. The EAG recommends an additional scenario analysis, using more realistic AE durations, using alternative AE disutilities for grade 3+ infusion-related reactions, and applying AE disutilities to grade 1 and 2 ARIA AEs.	High	The EAG recommends an additional scenario analysis, using more realistic AE durations, using alternative AE disutilities for grade 3+ infusion-related reactions, and applying AE disutilities to grade 1 and 2 ARIA AEs.	Further analysis	No further data collection possible / proposed	
EAG19	Cost and resource use discrepancies between the company's economic model and the NHS England Alzheimer's MCI model	Cost and resource use disparities were identified between the company's economic model and the NHS England Alzheimer's MCI model, including differences in unit costs, MRI safety monitoring, Aβ and ApoE4 testing, GP visits, quarterly outpatient reviews, and referral to local services	• The EAG adopted the IV infusion administration, lumbar puncture and PET-CT unit costs from the NHS England Alzheimer's MCI model in its base-case. • The EAG included 4 MRIs in the first year and 2 MRIs in every year thereafter for the modelling of lecanemab safety monitoring, in line with the NHS England Alzheimer's MCI model and the EAGs clinical expert comments. • The EAG performed a scenario analysis including ApoE4 test	High	An updated economic model including costs of GP visits, quarterly outpatients' reviews, ApoE4 testing and referral to local services.	Further analysis	No further data collection possible / proposed	It is plausible that some RWE could contribute here (none proposed)
EAG20	Inclusion of health state costs outside the NHS and PSS perspective on costs	Direct non-medical costs in the company's economic model included private care costs that fall outside the NHS and PSS perspective on costs	Exclude any costs outside of the NHS and PSS perspective on costs.	High	A different source to inform health state costs (if available), that includes a more transparent breakdown of the different cost components	Further analysis	No further data collection possible / proposed	

EAG21	Inconsistency between estimated outcomes with the company model and observed data from Clarity AD	In CS Tables 71 and 72 a comparison with the CS model and Clarity AD was made with regards to health state occupancy over time. The 18-month health state occupancy for the "Severe AD" health state is substantially overestimated. In response to clarification question B28, the company acknowledged "that the health state occupancy for the 'Severe AD' state is over-estimated in both the lecanemab and SoC arms of the model compared with the observed occupancy in Clarity AD".	Based on the current assessment, the EAG considers that the company's economic model does not accurately predict the state occupancy as observed in Clarity AD for both treatments and that there is a potential bias favouring the effectiveness of lecanemab. This might be related to the issue raised by the EAG in clarification question B10, i.e., potential technical errors in the estimation of transition probabilities to multiple health states and their conversion to a different period length matching the cycle length	Unquantified	Hence, this error should be corrected and subsequently the validation assessment be repeated.	Further analysis	No further data collection possible / proposed	
DG1	the distribution of change from baseline in CDR-SB score at 18 months, compared for lecanemab and placebo arms			Unquantified	No, data already collected	Further analysis of CLARITY	No further data collection possible / proposed	This data should have already been collected in the CLARITY trial and can be provided by the company. Company expects clinical practice data collection to record baseline characteristics per committee's request during any MAA period.
DG2	the mean difference from baseline by treatment arm at 18 months for the 6 individual domains of CDR-SB			Unquantified	No, data already collected	Further analysis of CLARITY	No further data collection possible / proposed	This data should have already been collected in the CLARITY trial and can be provided by the company. Company expects clinical practice data collection to record baseline characteristics per committee's request during any MAA period.
DG3	the least-squares mean change from baseline in EQ-5D-5L utility values, by treatment arm, analysed using a mixed effects model with repeated measures			Unquantified	No, data already collected	Further analysis of CLARITY	No further data collection possible / proposed	This data should have already been collected in the CLARITY trial and can be provided by the company. Company expects clinical practice data collection to record baseline characteristics per committee's request during any MAA period.
DG4	further information from clinical experts on what the introduction of lecanemab would do to the proportion of people who have MCI or mild dementia caused by Alzheimer's disease			Unquantified	Yes, information from the extension study, or from RWE could provide more information regarding the proportion of people with Alzheimers disease who do/do not have MCI or mild dementia.	CLARITY OLE	High	This data could potentially be collected if the trial continues. However there is uncertainty about the duration of the open label extension phase of the trial. RWE is also not a clear option for collecting information on this, as there are no existing robust RWE sources that could collect data for this indication. This can be considered an effectiveness uncertainty, so long-term data collection in the NHS may be helpful in resolving this uncertainty.
DG5	the distribution of the CDR-SB treatment effect for different subgroups that may have different treatment effects			Unquantified	No, data already collected	Further analysis of CLARITY	No further data collection possible / proposed	This data should have already been collected in the CLARITY trial and can be provided by the company. Company expects clinical practice data collection to record baseline characteristics per committee's request during any MAA period.
DG6	further information on the justification of constant transition probabilities and other approaches explored			Unquantified	Yes, information from the extension study, or from RWE could provide more information to support transition probabilities.	CLARITY OLE/RWE	High	While committee decision making may be enough to resolve this uncertainty, this data could also potentially be collected if the trial continues. However there is uncertainty about the duration of the open label extension phase of the trial. RWE is also not a clear option for collecting information on this, as there are no existing robust RWE sources that could collect data for this indication.
DG7	transition probabilities in the model that lead to outcomes and mortality benefit consistent with trial data and clinical expectations			Unquantified	No, this should be resolved by further modelling work.	N/A	High	TA are expecting to receive from company
DG8	a scenario analysis in which the model structure is revised so that each node only has 2 model transitions, to align with the first solution proposed by Gidwani et al. 2020			Unquantified	No, this should be resolved by further modelling work.	N/A	No further data collection possible / proposed	TA are expecting to receive from company
DG9	disaggregated, discounted and undiscounted results for the company's and EAG's base cases, by modelled health states			Unquantified	No, this should be resolved by further modelling work.	N/A	No further data collection possible / proposed	TA are expecting to receive from company
DG10	more information from the company on how the stopping rule on progression to moderate Alzheimer's disease would be applied in practice, including what measure would be used to determine progression and how often people would be assessed for progression			Unquantified	Maybe, information will be provided by the company, however there may be a benefit to a period of managed access in providing more information around progression.	CLARITY OLE/RWE	Medium	TA are expecting to receive from company, however more information from a period of managed access may help inform appropriate stopping times for patients who progress. RWE collection is not set up, but there is an ongoing trial (CLARITY OLE).
DG11	justification of how the stopping rule had been included in the modelling			Unquantified	No, this should be resolved by further information from company	N/A	No further data collection possible / proposed	TA are expecting to receive from company

DG12	scenarios exploring treatment waning for people who stop treatment because of all-cause discontinuation			Unquantified	No, this should be resolved by further modelling work.	N/A	No further data collection possible / proposed	TA are expecting to receive from company
DG13	scenarios exploring varying assumptions for the rate of all-cause discontinuation after 18 months			Unquantified	No, this should be resolved by further modelling work.	N/A	Medium	TA are expecting to receive from company. Company's managed access proposal expects this uncertainty to be resolved by data gathered in NHS practice.
DG14	detailed outline of the utility values used for each health state for both people with Alzheimer's disease and their carers, the data source for them and justification for that source, including considerations of proxy utility values and adaptation by people with Alzheimer's disease			Unquantified	No, this should be resolved by further information from company	N/A	No further data collection possible / proposed	TA are expecting to receive from company
DG15	a complete EAG critique of the final approach to model utility and disutility values			Unquantified	No, this should be resolved by further information from EAG	N/A	No further data collection possible / proposed	TA are expecting to receive from EAG
DG16	further information from the company and NHS England that fully explains estimated infusion costs and explores alternatives			Unquantified	Potentially, data could be collected for this uncertainty, however this is not currently set up.	May receive from company and NHS England/TA considered potential for managed access to benefit here	Medium	Data collection for costs is not currently set up, and it would be a large amount of work to establish this. Company's managed access proposal expects this uncertainty to be resolved by data gathered in NHS practice.
DG17	further information from the authors of the Alzheimer's Society report used to estimate direct non-medical costs on the proportion of costs that are private, or an alternative estimate of direct non-medical costs			Unquantified	Potentially, data could be collected for this uncertainty, however this is not currently set up.	May receive from company	Low	Data collection for non-medical costs is not currently set up, and it would be a large amount of work to establish this.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
Medium	There is one relevant trial and it is unclear whether it will continue collecting data after guidance is published. Anticipated completion date is 2027 but the decision problem form suggests that the OLE will only run until the technology receives marketing authorisation.

Clinical trial data - Clarity AD	
Anticipated completion date	Sep-27
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT03887455
Start date	Mar-19
Data cut presented to committee	NA
Link(s) to published data	https://www.nejm.org/doi/full/10.1056/NEJMoa2212948
Description of trial	An RCT assessing the efficacy and safety of lecanemab compared with placebo in participants with early Alzheimer's disease (EAD) over 18 months. An open label extension (OLE) will continue for 48 months in clinic until commercial availability of lecanemab and allows people on placebo to switch to treatment. Primary outcome for the core study is change from baseline in the CDR-SB at 18 months and in the extension phase change from core study baseline in CDR-SB. N=1906

Clinical trial data - BAN2401-G000-201	
Anticipated completion date	Feb-25
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT01767311
Start date	Dec-12
Data cut presented to committee	NA
Link(s) to published data	N/A
Description of trial	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. n=856 Dosages of lecanemab of interest: 2.5 mg/kg, 5.0 mg/kg, 10 mg/kg, bi-weekly or monthly.

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
Low	There are no existing, robust RWE sources set-up that could collect data for this indication. The company have suggested HES and audit data could be used to plug specific gaps but the data quality is likely to be low. It depends on what uncertainties the committee would want to address. Clinicians have indicated a willingness to gather data at regular consultations with patients. Blueteq could be used to gather baseline data on initiation with treatment. The decision problem form states: "Based on clinician's feedback, we anticipate data collection in the real-world to come from audit data from hospitals or independent research groups (e.g. UCL). Data could be collated using an organised national approach to cover collection of: patient demographics (including comorbidities, concomitant medications), reasons to initiate lecanemab, side effects monitoring, discontinuations and reasons for discontinuations, patient retention, effectiveness measurements (e.g. amyloid reduction or delay to next stage of disease), maintenance therapy post 18-months of treatment. We believe that NHS England may also have an interest in collecting data for NHS patients."

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	New	Blueteq for baseline information, other data remain unclear
Prior experience with managed access	Low	
Relevance of existing data items	Low	
If required, ease that new data items can be created / modified	Medium	
How quickly could the data collection be implemented	Unclear	
Data quality		
Population coverage	Medium	
Data completeness	Medium	
Data accuracy	Medium	
Data timeliness	Low	
Quality assurance processes	Unclear	
Data availability lag	High	
Data sharing / linkage		

New data sharing arrangements required?	Yes	
New data linkages required?	Yes	
If yes, has the governance of data sharing been established	Unclear	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	
If no, is there a clear process to develop the statistical analysis plan	Unclear	
Existing analytical capacity	Low	
Governance		
Lawful basis for data collection	Unclear	
Privacy notice & data subject rights	Unclear	
Territory of processing	Unclear	
Data protection registration	Unclear	
Security assurance	Unclear	
Existing relevant ethics/research approvals	Unclear	
Patient consent	No	
Funding		
Existing funding	No	
Additional funding required for MA	Yes	
If yes, has additional funding been agreed in principle	No	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	Unclear	
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		

Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	Yes	Additional assessments and appointments
Additional clinical burden	Yes	Additional assessments and appointments (though probably willing to take this on, require more resource)
Other additional burden	Yes	System implementation/rollout costs and risks, training etc

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Minor	High burden from any new data collection arrangements; implementation would be burdensome in routine commissioning and managed access; restricted implementation would go against IMF principles; complexity of topic would likely delay DCA development. Note this could be rated as Major but given Minor as NHSE has indicated they could include data collection and monitoring as part of new service set-up arrangements for this disease area given the forthcoming pipeline and political priority.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	High	Data collection within current practice does not exist and therefore there would be additional burden. Collection would need to be in primary and secondary care, which would be complex to implement.
	Expected overall additional system burden from data collection?	High	Data collection within current practice does not exist and therefore there would be additional burden. Collection would need to be in primary and secondary care, which would be complex to implement.
	Do stakeholders consider any additional burden to be acceptable	Unclear	NHSE could include data collection and monitoring as part of a service set-up for the disease area but consider set-up for a small number of drugs to be too burdensome.
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Yes	This is unclear

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?		TBC
	Is there a clear plan to monitor patient safety within a MA?		TBC
	Are additional patient safety monitoring processes required	No	Unlikely to require safety monitoring further than what would be expected in routine commissioning, but important to note there is no stopping rule.

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Unclear	IMF principles say that in the event of a negative recommendation at exit treatment will continue at the company's cost. The large budget impact may affect the company's willingness to enter managed access.
	If yes, have NHS England and the company agreed in principle to the exit strategy		TBC

		Rating	Rationale / comments

Service implementation	Is the technology disruptive to the service	No	Disruption would be the same for routine commissioning and managed access. Therefore, managed access would not subject system to additional burden, as things stand.
	Will implementation subject the NHS to irrecoverable costs?	Yes	Implementation through routine commissioning or managed access would be expensive and resource-intensive. This however is noted as a priority area for the NHS.
	Is there an existing service specification which will cover the new treatment?	Unclear	Service for this treatment would be a significant deviation to current care.

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	Unclear	Will depend on committee decision making. IMF principles dictate that the treatment needs to be made available to the entire eligible population for the indication.
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	No	Current discussions suggest implementation will be limited at first due to service capacity constraints
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	Unclear	There may be differences in how the drug would be rolled in managed access to routine commissioning but this is unclear
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Unclear	Difficult to assess for this indication
	Any issues from registry specific questions	Unclear	Yet to be determined/consulted

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	Unclear	Restricted implementation could have equality issues

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Unclear	What data could be collected would depend on how the drug is implemented, and if delayed would delay any DCA development