National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Eisai	This is an appropriate topic for NICE to consider as a single technology appraisal. There are currently no disease modifying therapies (DMT) for mild cognitive impairment or mild dementia caused by Alzheimer's disease (AD). The prevalence of this disease is rapidly increasing due to the aging population,1 leading to a substantial increase in related costs to the healthcare system, social care system, and to informal care. As such, there is high unmet need for DMTs such as lecanemab.	Comment noted. No changes to the scope are needed.
	NHS England	NHS England supports the evaluation and the proposed appraisal route.	Comment noted. No changes to the scope are needed.

Section	Stakeholder	Comments [sic]	Action
	Royal College of Psychiatrists	We think this is an important evaluation of significant clinical and public interest. Single technology appraisal would appear appropriate.	Comment noted. No changes to the scope are needed.
	Alzheimer's Research UK	It is appropriate to refer this topic to NICE for appraisal – if it is a cost-effective therapy for Alzheimer's disease it could significantly improve the health of a large patient population where there is significant unmet health need. There are currently no technologies available that delay or prevent the progression of Alzheimer's disease.	Comment noted. No changes to the scope are needed.
	Alzheimer's Society	We believe lecanemab could also be considered for fast track appraisal	Thank you for your comment. NICE aims to produce guidance within 90 days of the marketing authorisation being issued for a technology. In some instances, NICE will conduct streamlined cost-utility appraisals. However, this process is intended for simpler, low-risk topics where NICE has substantial previous experience of appraisals in the disease area.

Section	Stakeholder	Comments [sic]	Action
Wording	Eisai	Yes.	Comment noted. No changes to the scope are needed.
	NHS England	The wording does reflect the current issues for this patient cohort	Comment noted. No changes to the scope are needed.
	Royal College of Psychiatrists	Yes	Comment noted. No changes to the scope are needed.
Additional comments on the draft remit	Eisai	No comments.	Comment noted. No changes to the scope are needed.
	Royal College of Psychiatrists	Subject to any future market authorisation in the UK, we anticipate the evaluation will be eagerly anticipated by patients and professionals. This would represent the first disease modifying drug for Alzheimer's disease and the first ever treatment for MCI. We anticipate clinical services will need guidance on how best to offer this treatment, and that patients individually, or represented by the major dementia charities, will be looking for clarification on how NHS access to lecanemab will be determined and delivered. This will likely include how eligibility will be determined via access to appropriate biomarkers / imaging, how treatment will be delivered and how emergency and routine follow up, including any further imaging, should be provided. Given Alzheimer's disease is the leading cause of death in the UK and associated with such significant morbidity and economic cost, and the current	Comment noted. No changes to the scope are needed.

Section	Stakeholder	Comments [sic]	Action
		absence of a disease modifying treatment (DMT) for AD, a successful DMT would represent a major step forward in reducing stigma and offering hope to people with dementia. As such it would be a high priority for assessment for NHS delivery.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eisai	1. **Current wording:** "Differential diagnosis of Alzheimer's disease for people with mild cognitive impairment compared with other types of dementia is not always clearly defined." **Suggested wording:** "Differential diagnosis of Alzheimer's disease for people with mild cognitive impairment compared with other types of dementia is not always clearly defined. However, diagnostics used for AD dementia, such as positron emission tomography (PET) scan or cerebrospinal fluid (CSF) testing, can be used to differentiate MCI due to AD from MCI due to other causes." **Rationale:** Whilst diagnosis of MCI is not always clearly defined outside of Alzheimer's disease, MCI due to Alzheimer's disease can be clearly differentiated from MCI due to other causes through either an abnormal positron emission tomography (PET) scan or cerebrospinal fluid testing for amyloid beta protein.[2] 2. **Current wording:** "The number of people with dementia in England was estimated as 748,000 in 2019, with 107,100 cases of mild dementia. Therefore, the number of people diagnosed with mild dementia due to Alzheimer's disease could be up to around 80,000."	Thank you for your comments. Comment 1 and 3 suggested wording have been implemented in the scope. Comment 2: it is not standard practice to include estimated future patient numbers in scopes. Comment 4: it is not standard practice to highlight the absence of NICE guidelines. Existing NICE guidelines are

Section	Consultee/ Commentator	Comments [sic]	Action
		Suggested wording: "The number of people with dementia in England was estimated as 748,000 in 2019, with 107,100 cases of mild dementia. Therefore, the number of people diagnosed with mild dementia due to Alzheimer's disease could be up to around 80,000. It is projected that by 2040 the number of patients with dementia in England will rise by 81%, to 1,352,400, with 166,700 cases of mild dementia.[1]" **Rationale:** To recognise the rapidly increasing burden of dementia and Alzheimer's disease, due to a demographic shift into an aging population contributing to rapidly increasing incidence. 3. **Current wording:** "Current management of mild cognitive impairment and mild dementia due to Alzheimer's disease aims to improve cognitive, non-cognitive and behavioural symptoms and in some people may slow symptom progression." **Suggested wording:** "Current management of mild cognitive impairment and mild dementia due to Alzheimer's disease aims to improve cognitive, non-cognitive and behavioural symptoms, but does not slow progression of the underlying disease." **Rationale:** • Although currently available treatments, namely memantine, may slow symptom progression in some patients, evidence for this treatment is only available in moderate and severe stages of disease, which are outside the scope of this appraisal.[3] There is no evidence that these treatments slow symptom progression in patients with MCI due to AD or mild dementia due to AD. • Currently, there are no approved DMTs for Alzheimer's disease.	highlighted in the scope. Comment 5: it is no longer standard practice to include mechanism of action in scopes.

Section	Consultee/ Commentator	Comments [sic]	Action
		4. Current wording: "There is no pharmacological management of mild cognitive impairment due to Alzheimer's disease. Non-pharmacological management includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services, befriending services, day centres, respite care and care homes." **Suggested wording:** "There is no pharmacological management of mild cognitive impairment due to Alzheimer's disease, nor are there any recommended non-pharmacological management options or published NICE guidance for this group of patients.[4] Recommended non-pharmacological management for *mild to moderate dementia* includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services, befriending services, day centres, and in later stages of disease, respite care and care homes." **Rationale:** To clarify that there is no NICE guidance or NICE clinical guideline detailing interventions to be offered to patients with MCI due to AD. **5. Current wording:** "Lecanemab (Leqembi, Eisai Ltd) does not currently have a marketing authorisation in the UK. It has been studied in clinical trials compared with placebo in people with early Alzheimer's disease who meet the criteria for mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease." **Suggested wording:** "Lecanemab (Leqembi, Eisai Ltd) is a humanised monoclonal antibody that targets amyloid-beta (Aβ) proteins in the brain, a defining pathophysiological feature of Alzheimer's disease. Lecanemab	

Section	Consultee/ Commentator	Comments [sic]	Action
		has been studied in clinical trials compared with placebo in people with early Alzheimer's disease who meet the criteria for mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease. It does not currently have a marketing authorisation in the UK." **Rationale:** The draft scope does not detail the mechanism of action of lecanemab. In addition, the NICE scope for aducanumab for treating mild cognitive impairment and mild dementia caused by Alzheimer's disease [ID3763] included a description of the mechanism of action. 1. Wittenberg R, Hu B, Barraza-Araiza L, Rehill A. Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019–2040. 2019; 2. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):270–9. 3. Alzheimer's Society. Drug treatments for Alzheimer's disease. 2023; 4. Recommendations | Dementia: assessment, management and support for people living with dementia and their carers | Guidance | NICE [Internet]. NICE; 2018 [cited 2023 Mar 30]. Available from: https://www.nice.org.uk/guidance/ng97/chapter/Recommendations#interventions-to-promote-cognition-independence-and-wellbeing	
	Royal College of Psychiatrists	Accurate	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Neurologists	80,000 is a very conservative estimate of people living with mild dementia due to Alzheimer's disease	Thank you for your comment. The scope cites the 107,100 cases of mild dementia, which is adjusted by the reference citing up to 75% of dementia cases are due to Alzheimer's disease. This yields the figure of 80,000. As no other evidence has been shared, no changes to the scope have been made.
	Alzheimer's Society	Paragraph 1 Amendments: These can include mild problems with memory, reasoning, attention, language or **visuospatial function**. Alzheimer's disease usually develops slowly from these initial symptoms and progression is characterised by deterioration in cognition, functional ability and **associated behavioural and psychiatric symptoms**. Differential diagnosis of Alzheimer's disease **as the cause** for people **presenting** with mild cognitive impairment compared with other **causes of MCI is not straightforward from a clinical perspective**.	Thank you for your comments. The suggested amendments to paragraphs 1 and 4 have been implemented. The other suggested inclusions are not typically included in scopes.

		Paragraph 4 Correction on the use of memantine for moderate Alzheimer's disease, because: 1) Guidance TA217 mentions that memantine is recommended for people with moderate Alzheimer's disease 2) NG97 recommends dual therapy (memantine and CholEI) for people with moderate Alzheimer's disease Amendments: There is no pharmacological management recommended for mild cognitive impairment due to Alzheimer's disease. Non-pharmacological management for Alzheimer's disease dementia includes social support, Correction: The mention of the listed management methods are not appropriate for mild cognitive impairment, as most are used for moderate to severe dementia: use of social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services, befriending services, day centres, respite care and care homes Inclusions: • Dementia is the biggest cause of death in the UK • 25% of all hospital beds are taken up by someone with dementia • There are currently no disease modifying treatments (except in the USA)	

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Eisai	Yes.	Comment noted. No changes to the scope are needed.
	NHS England	NHS England welcomes further work being led by NICE, alongside other stakeholders, to refine population estimates. As noted above, NHS England believes that greater clinical and public awareness likely to be associated with the emergence of potential new treatment options may materially increase population estimates.	Comment noted. No changes to the scope are needed.
	Royal College of Psychiatrists	Yes	Comment noted. No changes to the scope are needed.
	Association of British Neurologists	Yes	Comment noted. No changes to the scope are needed.
	Alzheimer's Research UK	The population is defined as 'People with mild cognitive impairment or mild dementia due to Alzheimer's disease'. The challenge with that is: Mild Cognitive Impairment (MCI) is defined as a syndrome, and therefore this population will have a significant proportion of people who do not have MCI due to Alzheimer's disease and will not progress to develop Alzheimer's disease. Clinical definitions and uses of MCI are variable. It will be important to define the MCI population carefully to ensure that all appropriate patients are included in the scope.	Thank you for your comment. The population is not MCI alone, and therefore does not include people who have MCI not due to Alzheimer's disease, it is people with MCI due to Alzheimer's disease (or mild

Section	Consultee/ Commentator	Comments [sic]	Action
			dementia due to Alzheimer's disease).
Subgroups	Eisai	No comments.	Comment noted. No changes to the scope are needed.
	NHS England	NHS England would welcome examination of the evidence regarding whether some patients within the scope of a future market authorisation might derive greater benefit than others; this might assist the NHS to appropriately focus and prioritise its initial deployment strategies	Thank you for your comment. NICE's remit is to evaluate technologies within populations outlined in the marketing authorisation. This therefore excludes potential future indications not currently included in the marketing authorisation.
	Royal College of Psychiatrists	We are of the opinion it would be prudent to explore the relevance of subgroup differences – evidence permitting. According to additional published subgroup analysis, there is a need to evaluate whether additional factors could impact of both clinical effectiveness and risk of adverse events of lecanemab. For example: In terms of clinical efficacy - in the supplementary appendix to the phase III trial (van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948) participants who were non-carriers of the ApoE4	Thank you for your comment. The scope has been updated to include "ApoE4 carrier status" (evidence permitting) and the separate subgroups for mild cognitive impairment due to Alzheimer's disease

Section	Consultee/ Commentator	Comments [sic]	Action
		genotype, male and over 75 years had significantly higher adjusted mean differences in the primary outcome measure (clinical dementia rating-sum of boxes) versus placebo. For risk of adverse events – in the presentation of the *Clarity AD: A Phase 3 Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study Evaluating Lecanemab in Early Alzheimer's Disease Clinical Trials on Alzheimer's Disease (CTAD) San Francisco, CA, USA November 29 – December 2, 2022* - participants treated with lecanemab who were homozygous for ApoE 4 gene had more amyloid-related imaging abnormalities – oedema (ARIA-E) than those who were non-carriers (32.6% vs 5.4%). Higher prevalence of ARIA-haemorrhage (ARIA-H) were also seen in ApoE 4/4 carriers vs non-carriers (39% vs 11.9%). In the supplementary appendix of the Clarity trial there may be a signal of differential response between ethnic groups (eg CDR-SB – Asian = -0.35; white -0.49; black -0.72): even if there is currently insufficient evidence to determine differential responses between ethnic groups – if lecanemab is made available, post marketing monitoring access and response by group would be important. Finally – for example – in the USA the "criteria of use" for lecanemab by the Veterans Affairs (as recommended by their VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives) not only included the established exclusion criteria as used the phase III lecanemab trial – but also added "subgroup" exclusion criteria including being homozygous for ApoE4 genotype and aged below 65 years. (Ref https://www.va.gov/formularyadvisor/DOC_PDF/CFU_Lecanemab-irmb_LEQEMBI_CFU.pdf)	and mild dementia due to Alzheimer's disease. It is not appropriate to include subgroups based on ethnicity as this is a protected characteristic. However, the committee will consider equalities issues where evidence is presented.

Section	Consultee/ Commentator	Comments [sic]	Action
		In addition consideration might be given to those with 'MCI-AD' (including biomarkers) versus established Alzheimer's disease. Including the former would increase the numbers receiving treatment and may increase the demands on NHS memory clinics for assessment.	
	Association of British Neurologists	Early onset (<65) dementia might be examined separately due to greater costs of disease on families, more likely to have amyloid pathology confirmed, perhaps more tolerant of monitoring, less likely to die of other conditions and more likely to see longer term benefits, also they have fewer comorbidities eg anticoagulation that might affect risks	Thank you for your comment. Early onset dementia is defined by age and age is a protected equality characteristic. However, the committee will consider equalities issues where evidence is presented.
	Alzheimer's Society	There is one group that should be managed separately: People with Down's syndrome, as they are universally amyloid positive by mid-life. Since studies in this group, have not been undertaken, safety and efficacy is not known.	Comment noted. No changes to the scope are needed. The committee will consider equalities issues where evidence is presented.
Comparators	Eisai	Yes.	Comment noted. No changes to the scope are needed.
	NHS England	The comparators are appropriate.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Psychiatrists	Yes – see additional comments in response to consultation questions	Comment noted. No changes to the scope are needed.
	Association of British Neurologists	Yes	Comment noted. No changes to the scope are needed.
	Alzheimer's Research UK	The current comparators are recommended for people diagnosed with mild Alzheimer's (NICE 2018). However, the trial population was also for people with mild cognitive impairment and amyloid positivity. There are no established clinical guidelines in the UK regarding use of AChE inhibitors or memantine for people with MCI due to Alzheimer's disease.	Thank you for your comment. The comparators in the scope do not indicate AChE inhibitors or memantine for people with MCI due to Alzheimer's disease. Comparators in the scope are also indicated as "not limited to" so exact comparators can be determined by the committee.
Outcomes	Eisai	Eisai requests that HRQoL outcomes encompass both patient and caregiver HRQoL. Providing care for a patient with AD negatively impacts caregivers' psychological and physical health, can lead to social isolation, and can cause high levels of stress, which impact the quality of life of the caregiver.[5,6]	Thank you for your comment. The scope already includes health related quality of life as an outcome. This

Section	Consultee/ Commentator	Comments [sic]	Action
		Numerous studies have documented the substantial impact that caregiving has on caregiver quality of life.[7] 5. Dementia in the Family: The impact on carers [Internet]. Alzheimer's Research UK. [cited 2023 Apr 17]. Available from: https://www.alzheimersresearchuk.org/about-us/our-influence/policy-work/reports/carers-report/ 6. Alzheimer's Society. Caring for carers: Carer quality of life | Alzheimer's Society [Internet]. [cited 2023 Apr 17]. Available from: https://www.alzheimers.org.uk/Care-and-cure-magazine/Autumn-18/caring-carers-carer-quality-life 7. Weitzner MA, McMillan SC, Jacobsen PB. Family Caregiver Quality of Life: Differences Between Curative and Palliative Cancer Treatment Settings. Journal of Pain and Symptom Management. 1999 Jun 1;17(6):418–28.	includes carer quality of life.
	NHS England	It is noted that some clinical trials use proxy indicators as their primary or composite outcome measures and this will need to be taken into account in considering the evidence of clinical efficacy. The NHS will be keen to better understand the benefit the new treatments may be able to offer and whether these are clinically material i.e. equivalent to a MCID (minimally clinically important difference)	Comment noted. No changes to the scope are needed.
	Royal College of Psychiatrists	Yes	Comment noted. No changes to the scope are needed.
	Association of British Neurologists	Social care burden (including costs, carer QoL), and healthcare resource use would potentially be appropriate to capture. There may also be an effect on neuropsychiatric symptoms that could be an important determinant of QoL.	Thank you for your comment. The scope already includes health related quality of life as an outcome. This

Section	Consultee/ Commentator	Comments [sic]	Action
			includes carer quality of life. Healthcare resource use will also be considered in the economic modelling. Costs outside of the NHS and Personal Social Services perspective fall outside of the reference case set out in NICE health technology evaluations: the manual. The manual notes that some technologies may have substantial benefits to other government bodies. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care

Section	Consultee/ Commentator	Comments [sic]	Action
			and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website. No action required.
	Alzheimer's Research UK	Given the disease profile, it is important NICE considers the effect of the treatment on health-related quality of life (QoL) of the carer. There are an estimated 700,000 informal carers caring for those living with dementia in the UK , and the annual economic cost of dementia to society due to informal care is £10.2 billion . Dementia effects carers both mentally and physically. As well as having a major impact on daily living activities, we know informal carers are at a significant risk of depression and anxiety, leaving many socially isolated . Additionally, 48% of carers have a long-standing illness or disability . Given the impact that dementia has beyond the person with a disease such as Alzheimer's, and especially on carers, we believe carer health related quality of life (QoL) should be considered in a future appraisal to accurately assess the full value of a future treatment.	Thank you for your comment. The scope already includes health related quality of life as an outcome. This includes carer quality of life.

Section	Consultee/ Commentator	Comments [sic]	Action
		NICE has previously taken into consideration carer health related QoL in their economic analysis for symptomatic treatment of Alzheimer's disease and should do so in this case. Benefits will potentially be shown in the long-term, particularly as greater care costs are associated with the later, moderate to severe stages of dementia, and will prove challenging to evaluate over the relative short-time period of the phase III clinical trials. Flexibility in cost-effectiveness assessment should be considered given the inherent nature of this data uncertainty. Over 60% of dementia carers are also women , presenting the case that a socially equitable consideration of quality of life must factor those of the carer. Lewis et al (2014). Trajectory of Dementia in the UK – Making a Difference, report produced the Office of Health Economics for Alzheimer's Research UK, available on the ARUK Stat's Hub Luengo-Fernandez, R. & Landeiro, F. (in preparation). The Economic Burden of Dementia in the UK. Alzheimer's Research UK, 2015, Dementia in the Family, available: https://www.alzheimersresearchuk.org/wp-content/uploads/2019/09/Dementia-in-the-Family-The-impact-on-carers1.pdf Personal Social Services Survey of Adult Carers in England, 2016-17; NHS Digital Women and Dementia: A Marginalised Majority by Alzheimer's Research UK, available on the ARUK Stat's Hub	
	Alzheimer's Society	Amendment: • non-cognitive symptoms (e.g. behavioural and psychiatric symptoms)	Thank you for your comment. The suggested amendment has been made. The

Section	Consultee/ Commentator	Comments [sic]	Action
		Inclusions: Quality of life of carers (non-professional) Level of care received at home	scope already includes health related quality of life as an outcome. This includes carer quality of life and any impact therefore of the level of care received at home.
Equality	Eisai	No equality issues have been identified.	Comment noted. No changes to the scope are needed.
	Royal College of Psychiatrists	We are not aware of any specific concerns. Clearly it is important patients with Alzheimer's disease have parity of access to monoclonal antibody treatments c/w other diseases where they are used if they are supported by the evidence and have regulatory and NICE approval. If managed access is decided – and should this be offered via regional centres – then it would be important this does not create inequity of access (eg by virtue of geography, socioeconomic characteristics etc), particularly as these characteristics often co-localise with disparities in ethnicity. It would be important to monitor equity of access (and ideally response) to this treatment including by ethnic minorities and areas of deprivation including remote and rural areas.	Comment noted. No changes to the scope are needed. The committee will consider equalities issues where evidence is presented.
	Association of British Neurologists	People with mild dementia or mild cognitive impairment due to Alzheimer's disease are not routinely tested for amyloid pathology in the NHS. A large majority are diagnosed and treated in psychiatry-led services where the delivery of infusions and monitoring would be challenging. This means that there is a high risk that existing geographical and demographic inequalities in	Comment noted. No changes to the scope are needed. The committee will consider

Section	Consultee/ Commentator	Comments [sic]	Action
		access to a diagnosis of Alzheimer's disease will become inequalities in access to a disease-modifying treatment. The draft scope should ideally set out to address inequalities as a key part of the evaluation, and to quantify effects on health equity as part of the economic analysis.	equalities issues where evidence is presented.
	Alzheimer's Research UK	Limited access to PET scans and CSF for confirmation of amyloid positivity, diagnostic service capacity constraints, and inconsistencies in clinical expertise will lead to inequitable access to treatment delivery. It is unlikely that services across the UK, or even within England, will be uniformly ready to treat and manage patients on lecanemab if and when it becomes available. Patient access will be inequitably distributed along geographic and demographic lines if these challenges are not addressed. Much of current molecular biomarker diagnostic access is located within predominantly neurology led research centres, with access through research studies rather than NHS service delivery. This division in access by clinical specialty could add to geographical inequity in diagnostics. Findings from the Dementia Attitudes Monitor show that people from black, Asian and minority ethnic backgrounds are more likely to agree that 'dementia is an inevitable part of ageing' . Survey results also indicated that those from social grades DE (semi-skilled and unskilled manual workers, and those with no formal qualifications, state pensioners, casual and lowest grade workers, unemployed with state benefits only) were also more likely to agree with the statement. Less understanding and awareness of the diseases that cause dementia could result in people being less likely to come forward to seek diagnosis and treatment. Discussion of equality issues relating to the target condition should include the consideration that there is higher prevalence of dementia in women, and over 60% of dementia carers are women .	Comments noted. No changes to the scope are needed. The committee will consider equalities issues where evidence is presented.

Section	Consultee/ Commentator	Comments [sic]	Action
		Other populations that are particularly impacted by dementia include individuals with Down's syndrome. The lifetime risk of Alzheimer's disease in people with Down's syndrome is more than 90% and is the leading cause of death in this population . The predictable development of Alzheimer's neuropathology in people with Down's syndrome, most easily explained by overproduction of the amyloid-beta protein, means that this population are likely to benefit from an anti-amyloid treatment. Additional consideration may be needed to prescribe this medication to people with Down's syndrome. It is possible that there will be limited evidence on how people with Down's syndrome tolerate the technology used to administer the drug and monitor outcomes. The inclusion of people with disabilities in clinical trials and research is often overlooked. Restrictions in place for the safe-guarding of vulnerable adults often puts people off taking part in research. With the right support and research study design, people with Down's syndrome can, with the support of their family members and carers, provide informed consent and effectively take part in research. Azheimer's Research UK, 2018, Dementia Attitudes Monitor Wave 1, available: https://www.dementiastatistics.org/wp-content/uploads/2019/02/Dementia-Attitudes-Monitor-Wave-1-Report.pdf#zoom=100 Women and Dementia: A Marginalised Majority by Alzheimer's Research UK, available on the ARUK Stat's Hub McCarron M, McCallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down	

Section	Consultee/ Commentator	Comments [sic]	Action
		syndrome. J Intellect Disabil Res. 2017 Sep;61(9):843-852. doi: 10.1111/jir.12390. Epub 2017 Jun 29. PMID: 28664561. Hithersay, R., Startin, C. M., Hamburg, S., Mok, K. Y., Hardy, J., Fisher, E. M. C., Tybulewicz, V. L. J., Nizetic, D., & Strydom, A. (2019). Association of Dementia With Mortality Among Adults With Down Syndrome Older Than 35 Years. JAMA Neurology, 76(2), 152-160. https://doi.org/10.1001/jamaneurol.2018.3616	
Other considerations	Eisai	A broader perspective on costs should be considered, to include informal care outside of the NHS and Personal Social Services perspective, such as unpaid care by family/friends, out-of-pocket costs and loss of productivity. The economic burden of AD is substantially broader than the impact on the healthcare and social care systems, and the majority of the financial burden of AD is attributable to social and informal care. In 2019, the estimated total cost of dementia care in England was £29.5 billion, of which just 14% was attributable to healthcare, while 46% was attributable to social care, and 40% attributable to unpaid care.[1] As such, the introduction of a disease modifying therapy may alleviate some of the substantial financial burden on patients and caregivers. These benefits would not be captured within the current economic analysis framework. 1. Wittenberg R, Hu B, Barraza-Araiza L, Rehill A. Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019–2040. 2019;	Thank you for your comment. Comment noted. Costs outside of the NHS and Personal Social Services perspective fall outside of the reference case set out in NICE health technology evaluations: the manual. The manual notes that some technologies may have substantial benefits to other government bodies. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant

Section	Consultee/ Commentator	Comments [sic]	Action
			government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website. No action required.
	NHS England	NHS England would encourage the appraisal to consider the significant impact of the availability of a disease modifying treatment, such as lecanemab, on service delivery. There will be substantial infrastructure development required to support implementation of a positive NICE recommendation. The appraisal should consider the associated service requirements that are required to support access to this therapy:	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		• additional costs of MCI initial assessment in primary and community settings that are likely to be brought about through treatment availability and increased public awareness • capacity and costs associated with diagnosis and confirming eligibility for treatment • administration of the therapy (capacity and associated costs) • on-going monitoring, including any routine follow up PET-CT and MRI requirements (capacity and costs) NHS England would encourage the appraisal to identify whether there is evidence, which may influence the service requirements: • for continued treatment beyond the periods covered by trial evidence to inform dosing, expected duration of treatment and stopping criteria • that would support the use of lumbar puncture over amyloid PET-CT, or vice versa, for particular patients as the likely confirmatory diagnostic options ahead of any further validation of biomarker options	
	Alzheimer's Research UK	A true perspective of the full value of a treatment must also consider that dementia is different from many other disease areas in that costs are primarily picked up by individuals and families, not the state. This is driven by the relatively high prevalence of the disease and also the lack of treatment options. 1.1 billion hours are spent on unpaid informal care for dementia12, and recent economic modelling suggests this equates to £10.2 billion12. In comparison, 342 million hours were spent on unpaid informal care for cancer, 618 million hours for coronary heart disease, and 450 million hours for stroke care . It could be many years before the full benefit of the technology for people living with dementia, their carers, and wider society are fully understood.	Thank you for your comment. Comment noted. Costs outside of the NHS and Personal Social Services perspective fall outside of the reference case set out in NICE health technology evaluations: the manual. The manual notes that some technologies may have

Section	Consultee/ Commentator	Comments [sic]	Action
		Wider societal value will come in the form of keeping people out of supported care and in better health for many more years than is the present case. Approximately 55% of people living with dementia are in the mild stages, with 32% in the moderate stages and 12% in the severe stages . Slowing the progression of disease between the mild and severe stages of Alzheimer's would reduce the number of people requiring care who are living with Alzheimer's and present a cost benefit to the wider economy. Focusing narrowly on direct healthcare costs and benefits, with only limited consideration of social care and informal care costs, could result in an inaccurate assessment of the true value of the technology. Economic modelling with the London School of Economics showed that the full value of a disease modifying treatment for Alzheimer's disease is only demonstrated when a broader perspective of the savings across sectors, over time, is considered . More than a quarter of people with dementia are in care, and this has an annual cost to the economy of £10.8 billion. 60% of people receiving home-care services are living with dementia . In England and Wales, the number of people living with dementia who need palliative care will almost quadruple by 2040 . Landeiro, F, Luengo-Fernandez, R, 2021 [in preparation], 'Economic burden of cancer, CHD, dementia, and stroke 2018' Prince, M et al, 2014, Dementia UK: Update Second Edition report produced by King's College London and the London School of Economics for the Alzheimer's Society	substantial benefits to other government bodies. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Alzheimer's Research UK, 2018, Thinking Differently < https://www.alzheimersresearchuk.org/about-us/our-influence/policy-work/reports/thinking-differently-preparing-today-implement-future-dementia-treatments/> Luengo-Fernandez, R. & Landeiro, F. (in preparation). The Economic Burden of Dementia in the UK Carter, D (2015) Dementia and Homecare: Driving Quality and Innovation by the UK Homecare Association Etkind, S.N. et al (2017) How many people will need palliative care in 2040? Past trends, future projections and implications for services BMC Medicine 2017 15:102	
	Alzheimer's Society	We believe it should consider the impact on longer term outcomes. Such as the effect of slowing a disease over an 18 month period will have on the course of the dementia, not just in those 18 months	Thank you for your comment. The scope outlines that "the time time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared". The extent to which this is appropriate in the company submission

Section	Consultee/ Commentator	Comments [sic]	Action
			will be discussed by committee if it is considered relevant.
Innovation	Eisai	Yes. Substantial unmet need exists for a DMT for patients with AD (see response to *Draft Remit*). Subject to regulatory approval, lecanemab has the potential to be the first DMT for early AD and would represent a step-change in the management of these patients. Such a therapy could improve patient and caregiver HRQoL and reduce the considerable societal and direct cost burden associated with advanced stages of this disease, and prompt a paradigm shift towards early diagnosis to achieve disease slowing and to extend milder stages of disease.[8] 8. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. J Prev Alzheimers Dis. 2021;8(3):371–86.	Comment noted. No changes to the scope are needed.
Questions for consultation	Eisai	**Would lecanemab be used as an add on treatment to established clinical management? Would lecanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors?** **Comment/response:** Our current understanding is that lecanemab may be used as an add-on treatment to established clinical management, including AChE inhibitors for patients with mild dementia due to AD. **Have all relevant comparators for lecanemab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment or mild dementia caused by Alzheimer's disease?**	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Comment/response: Yes, all relevant comparators are included in the scope and represent those considered to be established in clinical practice. Please see comments in the *Background* and *Comparators* sections. **How should non-pharmacological management be defined?** **Comment/response:** Please see comments in the *Background* and *Comparators* sections. • For MCI due to AD: There is no published NICE guidance or clinical guideline for MCI due to AD. As such, non-pharmacological management for such patients is difficult to define and may differ from that for mild dementia due to AD and later stages of disease. • For mild dementia due to AD onwards: There is variability in the non-pharmacological management options offered to these patients, as summarised in the NICE guideline NG97 and the *Background* section of this draft scope. **The eligibility criteria for the clinical trial of lecanemab included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for lecanemab in clinical practice? Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?** **Comment/response:** Patients will require testing to confirm amyloid pathology, likely via a PET scan or CSF, to be eligible for treatment with lecanemab in clinical practice. PET scans are only available at specialist	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed. Thank you for your comment. The costs

Section	Consultee/ Commentator	Comments [sic]	Action
		centres and require the use of a radio tracer, which may not be widely available. CSF tests are cheaper, involve spinal puncture and administration of a specific biomarker dye. Due to the lack of DMTs, we are aware there are hurdles in access to diagnostics for early AD. Currently, patients with suspected mild cognitive impairment or mild dementia due to Alzheimer's disease are not routinely tested in the NHS for amyloid pathology. **Would lecanemab be a candidate for managed access?** **Comment/response:** Yes. **Do you consider that the use of lecanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Comment/response:** Yes. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** **Comment/response:** Lecanemab is expected to generate substantial added benefit, which may not be captured within the existing QALY framework due to the use of EQ-5D to estimate caregiver HRQoL. Caring for a patient with AD has a considerable burden on caregivers, and thus a negative impact on their quality of life. Delaying disease progression	associated with amyloid testing have been included in the updated scope. Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		for patients with AD will reduce burden on caregivers through delayed progression to later stages of disease, where patients require the most support.[9] The EQ-5D may not sufficiently capture these effects as it was not designed for use on caregivers and focusses on physical health.[10] Alternative measures specifically designed to assess caregiver burden, such as Zarit's Burden Interview (ZBI), more accurately capture the impact of caring for a person with AD. A statistically significant difference in change from baseline in ZBI was observed between lecanemab and placebo in CLARITY-AD, indicating alleviation of caregiver burden with lecanemab.[11] These health-related benefits may therefore not be adequately captured in the QALY calculation if EQ-5D is used to estimate caregiver HRQoL. 9. Georges J, Jansen S, Jackson J, Meyrieux A, Sadowska A, Selmes M. Alzheimer's disease in real life – the dementia carer's survey. International Journal of Geriatric Psychiatry. 2008;23(5):546–51. 10. Reed C, Barrett A, Lebrec J, Dodel R, Jones RW, Vellas B, et al. How useful is the EQ-5D in assessing the impact of caring for people with Alzheimer's disease? Health Qual Life Outcomes. 2017 Jan 21;15:16. 11. Eisai, 2022 Clarity AD CTAD Presentations. 2022: San Francisco, CA, USA.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Psychiatrists	**Q1: Would lecanemab be used as an add on treatment to established clinical management? Would lecanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors?** A1: Broadly we anticipate this would depend on stage of illness: • For people with a diagnosis of mild cognitive impairment due to Alzheimer's disease: o Lecanemab would be used solely as no other pharmacological treatment is licensed for this stage of Alzheimer's disease. • For mild dementia due to Alzheimer's disease: o Lecanemab most likely used in addition to AChEI. o Comment: Pragmatically treatment with AChEI will be far more straightforward and given their established prescribing status in the care of people with AD, AChEI are likely to be commenced "first-line" in the vast majority of patients. That said - given lecanemab and AChEI target different aspects of Alzheimer pathology, their comparative therapeutic roles could be seen "additional/complementary" rather than "alternative" to each other. **Q2: Have all relevant comparators for lecanemab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment or mild dementia caused by Alzheimer's disease?** A2:	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		• For people with a diagnosis of mild cognitive impairment due to Alzheimer's disease: o There are no licenced drug comparators o Comment: it is conceivable thresholds used by clinicians to distinguish MCI due to AD and mild dementia due to AD in clinical practice will vary, and though AChEI are not licenced for MCI per se, in situations where MCI is attributed to underlying Alzheimer's disease then AChEI may be more likely to be prescribed. • For mild dementia due to Alzheimer's disease: o Primarily this will be AChEI. o Comment: Occasionally in patients who are unable to tolerate AChEI or where they are contraindicated, Memantine may be prescribed as an alternative to AChEI in people with mild dementia due to AD (even though memantine is licenced for more advanced AD. **Q3: How should non-pharmacological management be defined?** A3: Broadly across the NHS, though there are examples of excellent practice, currently non-pharmacological interventions for people with MCI or mild dementia due to AD represent a collection of interventions under the umbrella term of "diagnostic counselling and support". This would include a variable amount of education, information, advice, signposting, psychosocial supportive interventions/social prescribing (eg	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		home or day care), and general health orientated recommendations such as exercise, nutrition, sensory assessments; compliance aids; primary care health checks. Currently there are no specific / evidenced based non-pharmacological treatments for MCI. For people with mild dementia (of any cause) cognitive stimulation therapy – usually delivered via structured 45-minute group therapy sessions twice a week over 7 weeks - may be offered to people with mild dementia (of any cause). Apart from Cognitive Stimulation therapy, there is also evidence to support Home based memory rehabilitation programme occupational therapy early intervention for people with dementia first established in Belfast City hospital in 2007 (McGrath & Passmore 2009). It is being offered to people with mild dementia (of any cause) **Q4: The eligibility criteria for the clinical trial of lecanemab included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for lecanemab in clinical practice? Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?** A4: • Yes we would expect amyloid positivity - determined by cerebrospinal fluid testing or PET imaging - would be a necessary (essential) criterion to be eligible. Reasoning includes:	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		○ Without this additional biomarker profiling it would be difficult to determine the potential contribution of Alzheimer pathology in people with clinical MCI. ○ Further, given the costs and risks associated with using lecanemab, it would be necessary to achieve the highest level of diagnostic confidence possible ○ Amyloid positivity should be established as this is consistent with the primary mode of action of lecanemab and was a requirement for entry to the pivotal clinical trials. Without knowing amyloid positivity the potential patient population would be significantly increased, with no data as to whether treatment might be effective for this expanded group. ○ Knowing the level of amyloid positivity also allows for monitoring of the biological outcome of using lecanemab. • Currently in routine clinical (noting the vast majority of patients with Alzheimer's disease in England are diagnosed and managed in mental health trusts with limited access to biomarker profiling) very few patients (outside of certain specialist centres or research studies) are tested for amyloid. We would estimate across the NHS no more than 5% of patients with AD are tested – indeed it more likely this is closer to less than 1% extrapolating from the findings of the RCPsych/ARUK national survey published in 2021 – https://www.rcpsych.ac.uk/members/your-faculties/old-age-psychiatry/are-we-ready-report . • Comment1: it would be important to only undertake amyloid testing in the context of someone presenting clinically with MCI or mild dementia	

Section	Consultee/ Commentator	Comments [sic]	Action
		to avoid over diagnosing, and by implication treating, AD purely on biomarker profiling alone. • Comment 2: If ApoE genotyping is required in context of subgroup typing – again currently this is not undertaken in routine clinical practice. • Comment 3: There is an appropriate use guidance for testing Amyloid PET CT in the 2022 fourth updated version of the Royal College of Physicians and Royal College of Radiologists published Evidence-based Indications for the use of PET-CT in the UK. The guidance comprises an up-to-date summary of relevant indications for the use of PET-CT where there is good evidence that patients will benefit from improved outcomes. They recommend Amyloid PET-CT be used where there is good evidence that patients will benefit from improved outcomes. They recommend there is now sufficient evidence to support the use of this technique in the scenarios defined by the appropriate use criteria, where the patient has persistent or progressive unexplained memory impairment not confirmed by standard medical tests, an unusual clinical presentation and/or an atypically early age of onset (usually defined as 65 years or less in age) ○ Johnson KA, Minoshima S, Bohnen NI et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. J Nucl Med Off Publ Soc Nucl Med 2013; 54: 476–490. ○ Carswell CJ, Win Z, Muckle K, Kennedy A, Waldman A, Dawe G et al. Clinical utility of amyloid PET imaging with (18)F-	

Section	Consultee/ Commentator	Comments [sic]	Action
		florbetapir: a retrospective study of 100 patients. J Neurol Neurosurg Psychiatry 2018; 89: 294–299. • It has been demonstrated that the introduction of amyloid brain PET in the investigative pathway has led to significant change in management and diagnosis therefore reducing the need for additional diagnostic testing. o Shea Y-F, Barker W, Greig-Gusto MT, Loewenstein DA, Duara R, DeKosky ST. Impact of Amyloid PET Imaging in the Memory Clinic: A Systematic Review and Meta-Analysis. J Alzheimers Dis JAD 2018; 64: 323–335. o de Wilde A, van der Flier WM, Pelkmans W et al. Association of Amyloid Positron Emission Tomography With Changes in Diagnosis and Patient Treatment in an Unselected Memory Clinic Cohort: The ABIDE Project. JAMA Neurol 2018; 75: 1062–1070. o Petersen RC, Lopez O, Armstrong MJ et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 90: 126–135. o Rabinovici GD, Gatsonis C, Apgar C et al. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. JAMA 2019; 321: 1286–1294 o Sevigny J, Chiao P, Bussière T et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016; 537: 50–56	

Section	Consultee/ Commentator	Comments [sic]	Action
		Q5: Are there any subgroups of people in whom lecanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately? A: Answered previously. **Q6: Would lecanemab be a candidate for managed access?** A6: There may be merit in this approach. In favour of this approach would be: o Limited readiness of general services to deliver this treatment – including access to biomarkers, necessary infrastructure, and staff training/expertise. Delivery of monoclonal antibody therapies is not new to the NHS – and there are many examples (including multiple sclerosis) where over time services have adapted and developed to deliver these treatments safety and effectively – but this mode of treatment would be new to be a mental health services and it will take time to build the necessary infrastructure, expertise and care pathways. o Currently the are no pharmacological treatment pathways for people with MCI due to Alzheimer's disease – so additional capacity would be required to manage this development. NHS memory clinics struggle to cope with existing rates of referrals, treatment for MCI may significantly increase the demand for diagnostic services. o Linked to this is the need to develop clear diagnostic framework to ensure the right people receive the intervention – diagnosing Alzheimer's disease before dementia is potentially a complex clinical task where the clinical and biomarker toolkit needs developing. o The costs and complexity of administrating i/v medication o The cost, expertise and access to biomarkers / MRI scans for safety monitoring will be important along stop/start algorithms to manage	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		ARIA and in and out of hours provision to manage emergency presentations. ○ The need for integration between mental health and acute hospital services especially in England. **Q7: Do you consider that the use of lecanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** A7: Currently data regarding the long-term benefits of disease modification with lecanemab is lacking – though modelling suggests if disease progression can be delayed substantial benefits in terms of morbidity, care needs, carer burden, admission to care, economic cost and mortality could result (Ref - The Value of Delaying Alzheimer's Disease Onset - PubMed (nih.gov)). **Q8: Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** A8: • A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Swanson et al. Alzheimer's Research & Therapy 2021; 13:80 • Lecanemab in Early Alzheimer's Disease. Christopher H. van Dyck et al N Engl J Med 5th Jan; 2023; 388:9-21 plus supplementary appendix.	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Supplement to: van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948 • Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Eric McDade, Jeffrey L. Cummings, Shobha Dhadda, Chad J. Swanson, Larisa Reyderman, Michio Kanekiyo, Akihiko Koyama, Michael Irizarry, Lynn D. Kramer and Randall J. Bateman. McDade *et al. Alzheimer's Research & Therapy (2022) 14:191* • Zissimopoulos J, Crimmins E, St Clair P. The Value of Delaying Alzheimer's Disease Onset. Forum Health Econ Policy. 2014 Nov;18(1):25-39. doi: 10.1515/fhep-2014-0013. Epub 2014 Nov 4. PMID: 27134606; PMCID: PMC4851168. • https://www.rcpsych.ac.uk/members/your-faculties/old-age-psychiatry/are-we-ready-report	
	Association of British Neurologists	1. *Would lecanemab be used as an add on treatment to established clinical management?* Yes: as an add on treatment 2. *Would lecanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors?* As an addition	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		3. *Have all relevant comparators for lecanemab been included in the scope?* YES 4. *Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment or mild dementia caused by Alzheimer's disease?* AChE inhibitors, non-pharmacological 5. *The eligibility criteria for the clinical trial of lecanemab included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for lecanemab in clinical practice?* YES 6. *Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?* NO 7. *Are there any subgroups of people in whom lecanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately?*	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		EARLY ONSET (<65) DEMENTIA MIGHT BE EXAMINED SEPARATELY DUE TO GREATER COSTS OF DISEASE ON FAMILIES, MORE LIKELY TO HAVE AMYLOID PATHOLOGY CONFIRMED, PERHAPS MORE TOLERANT OF MONITORING, LESS LIKELY TO DIE OF OTHER CONDITIONS, MORE LIKELY TO SEE LONGER TERM BENEFITS AND HAVE FEWER COMORBIDITIES EG ANTICOAGULATION THAT MIGHT AFFECT RISKS 8. *Would lecanemab be a candidate for managed access?* YES 9. *Do you consider that the use of lecanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* IT COULD LEAD TO IMPROVEMENTS IN RELATIONSHIPS, PSYCHIATRIC MORBIDITY AND CARER BURDEN THAT MIGHT NOT OTHERWISE BE INCLUDED	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.
	Alzheimer's Research UK	**Would lecanemab be used as an add on treatment to established clinical management? Would lecanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors?** Given the likely diagnostic requirements (amyloid positivity via CSF sample, amyloid PET scan or potentially a blood test), the likely profile of patients (younger, mild symptoms) and the requirement for regular MRI scanning and access to infusion suites, we would describe this as a new pathway for diagnosis and management of Alzheimer's disease.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Lecanemab likely would be used in addition to AChE inhibitors for people with mild Alzheimer's disease. Lecanemab trials allowed the concurrent administration of symptomatic anti-dementia therapies (cholinesterase inhibitors and memantine) . Previously approved AChE inhibitor treatments are used for symptomatic treatment, as opposed to having an effect on underlying disease progression. One of the two current classes of those treatments, memantine, is only licensed for moderate to severe AD as it is ineffective in mild dementia. There is no pharmacological management of mild cognitive impairment due to Alzheimer's disease currently. This further highlights the level of unmet need in treatment options for those with mild dementia. **Have all relevant comparators for lecanemab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment or mild dementia caused by Alzheimer's disease?** Yes, all relevant comparators for lecanemab have been included in the scope. There are no current disease modifying interventions available, only symptomatic for mild Alzheimer's disease and non-pharmacological interventions for both mild Alzheimer's disease and Mild Cognitive Impairment.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		The eligibility criteria for the clinical trial of lecanemab included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for lecanemab in clinical practice? Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS? Most people are currently diagnosed with Alzheimer's disease when they have overt clinical symptoms which can usually be identified using cognitive tests. To identify those people with MCI due to Alzheimer's disease or mild Alzheimer's disease the use of molecular biomarkers will be routinely required to determine amyloid positivity. Our expectation is that regulators would articulate this in their licence when providing guidance to prescribers. Diagnostic tests which are clinically validated are amyloid PET and CSF sample via lumbar puncture. They are recommended as a standard of care in NICE guidelines but are not currently commissioned as routine diagnostics across dementia services in England. In the 2021 Memory Assessment Services audit, only 2.2% of memory services had routine access to PET and CSF. In places where there is some access this is often via relationships with research institutions, often in neurology-led services. Access to these diagnostics is particularly difficult for Memory Assessment Services, which are predominantly led by Psychiatrists in Mental Health Trusts.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		The pathway will need to be able to diagnose people at a stage when clinical symptoms are less obvious. This will require changes to clinical practice, particularly in primary care, to ensure people at this stage of disease progression are referred appropriately. Lecanemab would also significantly alter the treatment component of the pathway in terms of drug delivery (i.e., additional intravenous infusion capacity) and ongoing monitoring of patients, through regular MRI scans. **Are there any subgroups of people in whom lecanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** It would be expected that, if given a license, the label would indicate that the drug would be suitable for those with mild cognitive impairment (MCI), or for those in the mild stage of Alzheimer's disease, with confirmed amyloid positivity, as per the trial population. MCI is described as a syndrome, and therefore this population will have a significant proportion of people who do not have MCI due to Alzheimer's disease and will not progress to develop Alzheimer's disease. Clinical definitions and uses of MCI are variable. It will be important to define the MCI population carefully to ensure that all appropriate patients are included in the scope . Clinical trials for lecanemab did not enrol patients in the moderate to severe stages of Alzheimer's disease, and it would not be expected that the technology would be suitable for that patient population. The patient population should initially consist of those in which efficacy and safety has already been studied. More long-term study follow up is required to increase	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		our understanding of whether particular sub-groups respond differently to the therapy. **Would lecanemab be a candidate for managed access?** Lecanemab definitely would be a candidate for managed access as there is an urgent unmet need in people living with MCI and mild dementia caused by Alzheimer's disease. There are currently no technologies available that delay or prevent the progression of Alzheimer's disease. As a first in class medicine in an area with a relatively large population, limited treatment options and significant investment in the existing pathway required to diagnose, administer and monitor the medicines, we recognise the challenges this poses to value assessment and wider concerns about affordability. Nonetheless we believe that given the high medical need and the wider impact to society it is important that the NHS provides national funding to any drug for Alzheimer's disease which is proven to be safe and efficacious. Phase III data shows lecanemab slowed the progression of the disease by 27%. More research is needed to confirm how the drug will perform in a real world setting if administered over a longer period of trial given, as the trial data looked at a carefully curated population of people over an 18-month period. A Managed Access Agreement would enable access to the therapy for people who will potentially benefit while uncertainty about the medicine's	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		longer term clinical effectiveness and/or cost-effectiveness are addressed by further data collection. **Do you consider that the use of lecanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** This treatment has the potential to bring value to people affected by this disease, their carers as well as wider society. The costs of Alzheimer's can be broadly split into healthcare, social care and informal care costs. In a HTA only healthcare and limited social care costs are considered. We believe all health, social and informal care costs of people living with Alzheimer's should be taken into consideration to assess the true value of this treatment. J. Cummings, L. Apostolova, G.D. Rabinovici, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alz Dis 2023; http://dx.doi.org/10.14283/jpad.2023.30 National audit of dementia Memory Assessment Services Spotlight Audit 2021, August 2022	Comment noted. No changes to the scope are needed.
	Alzheimer's Society	**Would lecanemab be used as an add on treatment to established clinical management? Would lecanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors?**	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Lecanemab should be used in addition, not an alternative for those with mild Alzheimer's disease. In treating MCI, it would be used as an alternative to AChE inhibitors as they have not been licensed to treat MCI **Have all relevant comparators for lecanemab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment or mild dementia caused by Alzheimer's disease?** Cognitive stimulation therapy is considered to be established clinical practice in the NHS for those with mild cognitive impairment. **Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?** In the National Memory Service Audit, 87% of services stated they could refer patients for DAT scans, 77% for PET scans and 56% for CSF examination.	Thank you for your comment. Cognitive stimulation therapy would be covered under non-pharmacological management as included in the scope. Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		However, in the case note audit, only 2% of patients were referred for one or more of these specialist investigations. **Do you consider that the use of lecanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The evaluation should consider longer term outcomes and the benefits on families and carers of people living with dementia. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** - Impact on carer related quality of life - longer term data about continued efficacy/impact on long term disease progression	Comment noted. No changes to the scope are needed. Comment noted. No changes to the scope are needed.
Additional comments on the draft scope	Eisai	No further comments.	Comment noted. No changes to the scope are needed.
	Alzheimer's Research UK	There will be significant service delivery impacts for the diagnostics and treatment components of the pathway which could be barriers to adoption. It should also be noted that multiple MRI scans will likely be required for monitoring of Amyloid Related Imaging Abnormalities (ARIA). Appropriate Use Recommendations (AURs) developed to assist in guiding the use of new agents such as lecanemab into clinical practice recommend obtaining MRIs within 1 year prior to initiation of treatment, prior to the 5th, 7th, 14th infusions and an additional week 52 MRI scan, especially for APOE4 genotype carriers and those with evidence of ARIA on earlier MRIs . Support to increase	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		capacity, both in terms of infrastructure, skills and capacity will be required. As this has the potential to be a first in class technology, we would anticipate high initial demand for access which would create particularly challenges for diagnostic services J. Cummings, L. Apostolova, G.D. Rabinovici, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alz Dis 2023; http://dx.doi.org/10.14283/jpad.2023.30	
	Alzheimer's Society	People with lived experience of Alzheimer's disease should be included in the process It is critical that: - Key criteria is provided to ensure the right volunteers are recruited i.e. the type of lived experience required - Clear instructions of what the involvement will consist of are provided - At least a month is given to allow the representatives to prepare	Thank you for your comment. Patient experts (including people with lived experience of Alzheimer's disease) are invited to make submissions, respond to technical engagement questions (if applicable) and make statements at committee meetings. NICE have a dedicated team from the Public Involvement Programme who will support members of the public through the process.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

None