National Institute for Health and Care Excellence

Health Technology Evaluation

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease ID6222
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Association of British Neurologists	Appropriate	Thank you for your comment.
	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 greatly 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. • The evaluation route proposed (single technology appraisal) is appropriate for evaluating this topic.	Thank you for your comment. No change to scope required.
	Eli Lilly	Lilly agrees that the single technology appraisal route is the most appropriate evaluation route for donanemab.	Thank you for your comment.

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	NHS England	NHS England (NHSE) supports the evaluation and the proposed appraisal route.	Thank you for your comment.
Wording	Eli Lilly	It is expected that donanemab will be given in addition to existing clinical management, with or without symptomatic pharmacological treatment, rather than displacing it. Therefore, Lilly proposes that the wording of the technology/intervention is changed from solely “donanemab” to “donanemab with best supportive care”.	Thank you for your comment. The intervention section has been amended to state donanemab with or without symptomatic treatments for Alzheimer’s disease.
	NHS England	NHSE would welcome financial modelling to include the costs of new referral and diagnostic pathways that would need to be introduced specifically to manage access to the treatment, as well as the costs of the drug and its administration for eligible patients, as this would more appropriately capture the overall costs of service delivery. In addtion, the costs of scans for both the monitoring and treatment of side effects should also be considered.	Thank you for your comment. The additional costs of introducing donanemab will be considered in the cost-effectiveness analysis of the technology appraisal. The costs and benefits of the outcomes (including adverse effects of treatment) will also be considered during the appraisal. .
Additional comments on the draft remit	Alzheimer’s Research UK	The remit suggests that the economic modelling should include the costs associated with diagnostic testing for amyloid and tau pathology in people with Alzheimer’s disease who would not otherwise have been tested.	Thank you for your comment. It is not within the remit of the scope to

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		Amyloid positivity is a key biomarker for people with early symptomatic AD and scaling CSF or introducing blood tests are more realistic than scaling of tau-PET scans. Based on Phase 2 data, the tau criteria led to the exclusion of patients with the highest tau levels, who are considered to have disease that is more resistant to anti amyloid treatment. The requirement for confirmed tau pathology will depend on MHRA decision on eligibility for donanemab. However, we think this decision needs to be pragmatic since there are no approved tau PET ligand tracers for use in the UK (only one tau PET scan is available in US, none in EU) and that diagnosis via amyloid detection is clinically appropriate.	specify which diagnostic testing should be used. The economic analysis section of the scope specifies this. The suitability of tau criteria will be discussed by the appraisal committee.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	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 wording has been amended to more clearly emphasise that this is an estimate.
	Alzheimer's Society	Dementia is one of the leading causes of death in the UK 25% of all hospital beds are taken up by someone with dementia There are currently no disease modifying treatments, approved for use in the UK	Thank you for your comment. The background section of the scope is intended to be a brief overview of the condition and current treatments.

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			Submissions for this appraisal can include much more detail. That there are currently no disease modifying treatments approved for use has been added to this section.
	Eli Lilly	The background information states that “the number of people diagnosed with mild dementia due to Alzheimer’s disease could be up to around 80,000.” People with suspected mild cognitive impairment or mild dementia caused by AD are not currently routinely tested for amyloid pathology within the NHS. Lilly therefore suggests that the following statement is added to the sentence: “however, many of these will not have been confirmed by biomarker tests.” Further, Lilly suggests adding a similar caveat to the statement that “with approximately 5% to 20% of people with mild cognitive impairment developing dementia, although there is variation in risk estimates” to read: “with approximately 5% to 20% of people with mild cognitive impairment developing dementia, although there is variation in risk estimates and this may differ in patients with biomarker confirmed mild cognitive impairment due to AD.”	Thank you for your comment. The background section of the scope is intended to be a brief overview, and not exhaustive. The background section has been amended to include the suggested caveat around the estimate of 80,000 diagnosed with mild dementia. Risk factor modification has also been added to the list of non-pharmacological interventions in the background section.

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		Lilly also suggests that the list of non-pharmacological management of AD is expanded to include risk factor modification. Overall, the remaining background information is broadly accurate.	
	NHS England	NHSE agree that the background information is accurate. We recognise what the course of progression is for those patients with MCI and amyloid, and tauopathy pathology, is not well known at this stage.	Thank you for your comment. No change to scope required.
Population	Association of British Neurologists	Yes [the population is defined appropriately]	Thank you for your comment.
	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 and NICE does not have a clinical guideline in place for management of people with MCI. 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 in the scope aims to be in alignment with patients in the clinical trial. The current wording stipulates that the MCI or dementia is due to Alzheimer's disease. No change to scope required.
	Dementia UK	Whilst those aged under 65 with mild cognitive impairment or mild dementia are included within the current definition, it should be noted that the background information predominantly focuses on those aged over 65. We	Thank you for your comment. The wording of the remit is inclusive

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		urge caution that those affected aged under 65 are therefore not left out of the TA process.	of all ages. The committee will consider equalities issues where evidence is presented. No change to scope required.
	Eli Lilly	The population is defined appropriately, donanemab is anticipated to be recommended for people with MCI due to AD or mild AD dementia	Thank you for your comment.
	NHS England	We acknowldege that whilst there are reports based on consensus as what is meant by MCI currently the way the diagnosis is used varies between care settings. Therfore, we would request the eligible population to be more robustly defined	Thank you for your comment. The population is intended to reflect those patients who were in the clinical trials. The appraisal will consider the technology within its marketing authorisation which is currently commercial in confidence. It is outside of the remit of the scope to account for how the MCI diagnosis varies in clinical practice. No change to scope required.

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Subgroups	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. The wording of the remit is inclusive of all ages. The committee will consider equalities issues where evidence is presented. No change to scope required.
	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 are not known.	Thank you for your comment. The wording of the remit is inclusive of all people. Further information on this can be included in your submission for consideration during the appraisal. The committee will consider equalities issues where evidence is presented. No change to scope required.
	Dementia UK	We have no comments on this aspect of the draft scope beyond the need to ensure that those aged under 65 are not excluded from the populations under consideration.	Thank you for your comment. The wording of the remit is inclusive of all ages. The committee will consider

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		However, we have concerns about how, should the treatment successfully make it through the TA, these population and subgroups under consideration will be reached in time to access the treatment. We also would be interested to include consideration of at what point would specialist screening for tau and amyloid be undertaken to ensure that protein markers are identified early enough to feed into diagnosis and treatment.	equalities issues where evidence is presented. It is outside of the remit of the scope to specify how diagnostic screening should be implemented in clinical practice. The economic analysis section of the scope specifies this. No change to scope required.
	Eli Lilly	Lilly will review the full clinical evidence once available and determine if any subgroups should be examined separately. If relevant, these subgroups will be presented and fully explored within the submission.	Thank you for your comment.
	NHS England	We 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 information would help assist the NHS to appropriately prioritise deployment strategies if required.	Thank you for your comment. Subgroups specified in the scope may be addressed in the technology evaluation if the evidence allows. No change to scope required.
Comparators	Association of British Neurologists	Yes [all relevant comparators have been included]	Thank you for your comment.

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	Alzheimer's Research UK	• Yes, the comparators listed are the standard treatments currently used in the NHS. • The current comparators are recommended for people diagnosed with mild Alzheimer's (NICE 2018). • 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. • Disease-modifying treatments (including donanemab) are not envisaged to replace symptomatic or non-pharmacological treatments. They will likely play a complementary role and therefore any comparison should be made cautiously.	Thank you for your comment. No change to scope required.
	Eli Lilly	NICE do not currently have a recommended treatment pathway for MCI and there are no treatments which can be considered established clinical practice within the NHS. The existing NICE guideline NG97 (published in June 2018) focuses on pharmacological treatment for mild, moderate and severe AD. Within NG97, AChE inhibitors are recommended for use for patients with mild AD dementia. Lilly requests that "best supportive care" rather than specific interventions should be used as a comparator. Non-pharmacological management with or without symptomatic pharmacological treatment should be considered add-ons to donanemab, in line with the design of the clinical trials of donanemab.	Thank you for your comment. The comparators section states 'Established clinical management without donanemab, including but not limited to: •For mild cognitive impairment due to Alzheimer's disease: - Non-pharmacological management

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		Therefore, donanemab is expected to be used alongside AChE inhibitors and as such, AChE inhibitors alone would not represent a relevant comparator in this submission and should be removed.	•For mild dementia due to Alzheimer's disease: - An AChE inhibitor plus non-pharmacological management. The intervention section of the scope has been amended to state donanemab with or without symptomatic treatments for Alzheimer's disease.
	NHS England	We would suggest considering additional comparators for: • drugs used in early MS • best supported care lecanemab (if appraisal is sufficiently advanced to enable donanemab to be compared)	Thank you for your comment. NICE does not consider that drugs used in early multiple sclerosis are routinely used in mild cognitive impairment or mild dementia caused by Alzheimer's disease. For consideration of best supportive care, please see response to previous comment. The lecanemab appraisal is not yet underway so cannot be

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			considered as a comparator. No change to scope required.
Outcomes	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. Non-cognitive symptoms has been included as an outcome. The scope already includes health related quality of life as an outcome. This 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

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			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.

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	Alzheimer's Research UK	***Health related carer quality of life*** • 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. • 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. NICE should provide clear guidance on how Committee's will consider caregivers' quality of life in the assessment process, including how to measure it. • 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	Thank you for your comment. All aspects of quality of life including carer quality of life will be considered in the evaluation if evidence allows. No change to scope required.

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		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.	
	Alzheimer's Society	Quality of life of carers (non-professional) Level of care received at home	Thank you for your comment. All aspects of quality of life including carer quality of life will be considered in the evaluation if evidence allows. No change to scope required.
	Dementia UK	For many, a diagnosis of dementia can mean fear and confusion, not only for the person with dementia, but also for the people caring for them and their wider family and friends. Individual and their families may live with the condition for many years during which every day can throw up new and complex challenges as individuals try to navigate a complex and disjointed health and social care system; trying to support someone with dementia can be exhausting and overwhelming. It is easy for family carers to become isolated as they put their own lives on hold - and take on a role that can push them to breaking point. We would therefore ask that the impact on families and carers is assessed within this TA as part of a holistic view of the health-related benefits for the individual living with dementia.	Thank you for your comment. All aspects of quality of life including carer quality of life will be considered in the evaluation if evidence allows. No change to scope required.

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		We also note that adverse effects of treatment will be assessed as an outcome, which we welcome and would hope that the TA seeks clarity on how any adverse effects are treated or managed both in the short and long term.	
	Eli Lilly	Lilly agrees that the outcomes listed are appropriate for this appraisal.	Thank you for your comment.
	NHS England	We would welcome consideration be given to: • the impact on carers and social care (which is where the main cost of care / burden falls). • do reported treatment effects outweigh safety concerns and are they generalisable to a representative clinical population of people with Alzheimer's disease. • how convincingly does the data suggest that there will be likely clinical benefit beyond the duration of the trials.	Thank you for your comment. All aspects of quality of life including carer quality of life will be considered in the evaluation if evidence allows. Treatment effect and adverse events will be taken into account in the economic analysis. 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

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			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

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			change to scope required.
Equality	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 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.	Thank you for your comment. Please see the accompanying EIA for further details. The committee will consider equalities issues where evidence is presented. No change to scope required.
	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 within England, will be uniformly ready to treat and manage patients with donanemab 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 largely through research studies rather than NHS service delivery. This division in access by clinical specialty could add to geographical inequity in diagnostics. • Findings from Alzheimer's Research UK's Dementia Attitudes Monitor show that people from black, Asian and minority ethnic backgrounds	Thank you for your comment. The committee will consider equalities issues where evidence is presented. No change to scope required.

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		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. • 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	

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		in research. With the right support and research study design, people with Down's syndrome can, with the support of their family members	
	Dementia UK	Dementia UK has concerns that there are considerable variations and inequalities within dementia diagnosis and support across England. Beyond significant regional variation in dementia diagnosis rates, there are further structural and cultural inequalities in diagnosis, symptom presentation and care amongst different populations. For example, a 2018 study found that black men developing dementia were less likely to be diagnosed than white men developing dementia. Previous research has also found that, symptoms of mental illness can be less frequent, less severe or different in BME older people consulting GPs. Symptoms have also been shown to be different in older people originating from the Indian sub-continent. In order to meet these needs, it would be good to consider how these groups may be able to access Donanemab. This should include what provision would need to be put in place to encourage early help seeking and diagnosis to ensure they begin the treatment pathway at an appropriate stage in their symptom progression. In addition, the successful application of Donanemab within NHS healthcare settings will require significant uplift in system preparedness, training and resource to ensure that any inequalities are not widened. Currently dementia diagnosis is delivered through memory assessment services and primary care. The existing services are experiencing significant pressures, and variability in service, with long waits for diagnosis. This presents two major issues that could exacerbate inequalities – the equal provision of the infrastructure needed, especially between urban and rural settings, or within	Thank you for your comment. The committee will consider equalities issues where evidence is presented. No change to scope required.

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		areas of socio-economic deprivation, and the suitability of the existing dementia workforce on delivering this treatment. We therefore encourage NICE to take system preparedness into account, with recommendations on how to ensure that there is fair access to this treatment that doesn't exacerbate inequality. We further would like the TA to look at how access to Donanemab will be monitored and reported on against geographical, socio economic and protected characteristics.	
	Eli Lilly	No equality issues have been identified.	Thank you for your comment.
	NHS England	NHSE would like to flag the importance of giving consideration to what are the characteristics of those who can benefit from the treatment and ensuring those offered treatment include those with protected characteristics. For example, where the sites are located that can administer the treatments could adversely impact certain groups who may not be able to afford to travel.	Thank you for your comment. The committee will consider equalities issues where evidence is presented. No change to scope required.
Other considerations	Alzheimer's Research UK	*Wider societal cost* ▪ 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 dementia, and recent economic modelling suggests this equates to £10.2 billion. 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.	Thank you for your comment. The technology evaluation will consider all evidence on costs and benefits in the economic model. Costs outside of the NHS and Personal Social Services perspective

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		▪ 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. 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.	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 and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the

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			recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website. No change to scope required.
	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. More data will be available on longer term outcomes from additional clinical trials.	Thank you for your comment. The technology evaluation will assess the available evidence. No change to scope required.
	NHS England	NHSE would encourage the appraisal to identify whether there is evidence: • 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 blood-based biomarker options. The appraisal should consider the associated service requirements that are required to support access to this treatment:	Thank you for your comment. The technology evaluation will assess the available evidence, including any evidence on treatment effect duration. The economic analysis will attempt to include evidence on associated implementation costs of diagnosis and treatment. No change to scope required.

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		• 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 treatment. • on-going monitoring, including MRI scans. • support requirements for family members whose relative is having this treatment and how stoping treatment will be handled.	
Questions for consultation	Association of British Neurologists	Yes: as an add on treatment *Would donanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors?* As an addition *Have all relevant comparators for donanemab been included in the scope?* YES *Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment or mild dementia caused by Alzheimer's disease?*	Thank you for your comments. The wording of the remit is inclusive of all ages. The committee will consider equalities issues where evidence is presented. No change to scope required.

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		AChE inhibitors, non-pharmacological *The eligibility criteria for the clinical trial of donanemab included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for donanemab in clinical practice?* YES *Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?* NO *Are there any subgroups of people in whom donanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately?* 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	

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	Alzheimer's Research UK	*Would donanemab be used as an add on treatment to established clinical management? Would donanemab 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), we would describe this as a new pathway for diagnosis and management of Alzheimer's disease. • Donanemab likely would be used in addition to AChE inhibitors for people with mild Alzheimer's disease. • 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 donanemab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for symptomatic early Alzheimer's disease?* Yes, all relevant comparators for donanemab have been included in the scope. There are no current disease modifying interventions available, only	Thank you for your comments. The suitability of tau criteria will be discussed by the appraisal committee. No change to scope required.

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		symptomatic for mild Alzheimer's disease and non-pharmacological interventions for both mild Alzheimer's disease and Mild Cognitive Impairment. We are aware that NICE is also due to look at the therapy lecanemab. While these drugs are both of the same class of treatment (anti-amyloid) we support NICE's decision to review separately particularly as the drug's target the amyloid protein in different ways. Disease-modifying treatments (including donanemab) are not envisaged to replace symptomatic or non-pharmacological treatments. We would expect them to have a complementary role and therefore any comparison should be made cautiously. *The eligibility criteria for the clinical trials of donanemab included that people should have confirmed amyloid and tau pathology. Is it expected that this will be a criterion for being eligible for donanemab in clinical practice? Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid and tau 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.	

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		▪ 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. ▪ Based on Phase 2 data, the tau criteria led to the exclusion of patients with the highest tau levels, who are considered to have disease that is more resistant to anti amyloid treatment. The requirement for confirmed tau pathology will depend on MHRA decision on eligibility for donanemab. However, we think this decision needs to be pragmatic since our understanding is that there are no approved tau PET ligand tracers for use in the UK (only one tau PET scan is available in US, none in EU). Amyloid positivity is a key biomarker for people with early symptomatic AD and scaling CSF or introducing blood tests are more realistic than scaling of tau-PET scans. ▪ 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. *Are there any subgroups of people in whom donanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately?*	

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		• 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. • 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 our understanding of whether particular sub-groups respond differently to the therapy. *Would donanemab be a candidate for managed access?* • Donanemab 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. • According to Eli Lilly, donanemab's Phase III data showed a key measure of cognitive and functional decline by 35% over 18 months. After a peer reviewed paper is published (we understand this will be at the Alzheimer's Association's International Conference in July), more data	

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		collection will be needed to confirm how the drug will perform in a real world setting if administered over a longer period of trial. • A Managed Access Agreement would enable access to the therapy for people who will potentially benefit while uncertainty about the medicine's longer term clinical effectiveness and/or cost-effectiveness are addressed by further data collection. *Do you consider that the use of donanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* • 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 NICE HTA only healthcare and limited social care costs are routinely 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.	
	Alzheimer's Society	Would donanemab be used as an add on treatment to established clinical management? Would donanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors? **Donanemab should be used in addition, not an alternative for those with mild Alzheimer's disease. In treating MCI, it would be used alone, without AChE inhibitors as they have not been licensed to treat MCI** The eligibility criteria for the clinical trials of donanemab included that people should have confirmed amyloid and tau pathology. Is it expected that this will be a criterion for being eligible for donanemab in clinical practise?	Thank you for your comments. The suitability of tau criteria will be discussed by the appraisal committee. No change to scope required.

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		As donanemab is an amyloid targetting therapy, it should be necessary to confirm amyloid positivity for eligibilty. This could be along with other tests to confirm that the patients do indeed have cognitive symptoms/brain atrophy associated with Alzheimer's disease. We know that there are people who have amyloid positivity in their brains but do not have cognitive symptoms. There is currently no data on whether removing amyloid in preclinical Alzheimer's disease can delay onset of symptoms. This is being explored in trials like TRAILBLAZER –ALZ3, but these trials have not yet produced or shared data. **In terms of using tau to define eligibilty – whilst tau deposition is believed to be better correlated with cognitive decline, it is not a primary target of the therapy.** **The topline data from the trial did show that donanemab showed the greatest effect in people with an intermediate level of tau in their brains, compared to the total cohort which also included those with high levels of tau deposition. The full data (due in July) may show how effective donanemab is for people with high levels of tau in their brains. Without this data, it is difficult to know how important tau pathology is to confirm eligibility.** Are there any subgroups of people in whom donanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately? **We are still awaiting the release of the full dataset for donanemab, which may include further breakdown of the drug's efficacy with regards to differences in sex or in ethnicity.** **From the topline data released, there was indication of a population of people living with mild cognitive symptoms, amyloid positivity but intermediate tau burden. This appears to be the population in which**	

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		donanemab was most effective at slowing progression of symptoms. This strengthens the idea that donanemab may be more effective, the earlier in the development of Alzheimer's disease pathology it is given. Would donanemab be a candidate for managed access? **Since only topline results have been released from the donanemab trial it is not currently possible for us to comment on a managed access recommendation as the clinical and cost effectiveness of the drug have not been fully shared publicly. We will know more once the full data are released on 17th July 2023**	
	Eli Lilly	Would donanemab be used as an add on treatment to established clinical management? Would donanemab be used in addition to AChE inhibitors or as an alternative to AChE inhibitors? It is expected that donanemab would be used alongside, rather than as an alternative to, AChE inhibitors for patients who have mild AD dementia. Background medications were permitted within the TRAILBLAZER-ALZ-2 trial and as such clinical evidence will be available within this patient population. Have all relevant comparators for donanemab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for symptomatic early Alzheimer's disease? As mentioned previously, NICE do not currently have a recommended treatment pathway for MCI. The existing NICE guideline NG97 (published in June 2018) focuses on pharmacological treatment for mild, moderate and severe AD. Within NG97, AChE inhibitors are recommended for use for patients with mild AD dementia. However, as noted above, donanemab is	Thank you for your comments. No change to scope required.

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		expected to be used alongside non-pharmacological treatment with or without AChE inhibitors and as such, AChE inhibitors alone would not represent a relevant comparator in this submission. Lilly agrees that all relevant comparators have been included within the scope. How should non-pharmacological management be defined? Non-pharmacological management is not expected to differ between the intervention and comparator arms, therefore Lilly does not expect this to be a key factor within the economic analysis. It is expected that costs associated with non-pharmacological management could be captured within the health state costs. The eligibility criteria for the clinical trials of donanemab included that people should have confirmed amyloid and tau pathology. Is it expected that this will be a criterion for being eligible for donanemab in clinical practice? Are people with suspected mild cognitive impairment or mild dementia caused by Alzheimer's disease routinely tested for amyloid and tau pathology in the NHS? The licence wording for donanemab is anticipated to specify that [redacted]	

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		[redacted] Currently, people with suspected mild cognitive impairment or mild dementia caused by AD are not routinely tested for amyloid or tau pathology within the NHS, as such testing would not change current clinical management in the absence of disease-modifying therapies which target amyloid. Are there any subgroups of people in whom donanemab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Lilly will review the full clinical evidence once available and determine if any subgroups should be examined separately. If relevant, these subgroups will be presented and fully explored within the submission. Would donanemab be a candidate for managed access? Given the novel and innovative nature of donanemab, Lilly expects that it could be a candidate for either routine commissioning or managed access. Do you consider that the use of donanemab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	

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		AD has a large impact on carers, friends and relatives. This treatment has the potential to bring value not only to people directly affected by this disease, but also their carers, friends and relatives. There may be challenges in fully capturing the impact on the health-related quality of life of carers, friends and relatives of people with MCI and mild AD dementia within the QALY calculation. In addition, work by Garrison et al. (2021) defines key elements of value in AD with the “AD value flower” outlining numerous elements of value, such as the value of knowing and of hope, which may be difficult to include quantitatively in the QALY calculation.	
	The Royal College of Pathologists	The eligibility criteria for clinical trials of Donanemab stipulate that patients should have confirmed amyloid and tau pathology. The document does not specify the test method. Most likely, this will be a non-invasive (imaging) or minimal invasive (CSF) procedure, rather than a brain biopsy. Regardless, it should be identified how patients will be tested, to assess the impact on pathology services (CSF, biopsy), or imaging services (Neuroimaging including tracers).	Thank you for your comment. It is outside of the remit of the scope to specify which diagnostic techniques should be used in clinical practice. The suitability of tau criteria will be discussed by the appraisal committee. No change to scope required.
Additional comments on the draft scope	Alzheimer’s Society	People with lived experience of Alzheimer’s disease should be included in the consultation process It is critical that:	Thank you for your comment. People with lived experience of Alzheimer’s disease will be invited to participate

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		- Key criteria is provided to ensure the right volunteers are recruited i.e. the type of lived experience required - Clear insructions of what the involvement will consist of are provided - At least a month is given to allow the representatives to prepare	in the technology evaluation in advance of the meeting and will receive help in participating. No change to scope required.
	Eli Lilly	Perspective on costs In terms of costs to be considered in the analysis, the company would also like to highlight the suitability of a non-Reference Case value framework capturing costs of informal care givers, and also out-of-pocket social care costs. The broader aspects of value associated with novel disease-modifying therapies for Alzheimer's Disease, particularly societal and informal care costs, should be considered within this appraisal. The company would value further advice from NICE as to the appropriate procedure to follow for NICE to be allowed to consider non-Reference Case perspectives in this appraisal.	Thank you for your comment. It may be appropriate to include a non-reference case value framework in this technology evaluation. This should be discussed at the decision problem meeting in the first instance. No change to scope required.

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

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