National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Biogen	This is an appropriate topic for NICE to consider.	Thank you for your comments. No action required.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	Highly appropriate, but only if it is given licensing authorisation by EME/MHRA. Dementia is a huge and growing burden, and Alzheimer's disease is the cause in around 2/3 cases. There are only 4 symptomatic drugs available for Alzheimer's disease, and none are licensed for mild cognitive impairment. The availability of a disease modifying drug would potentially be a major advance, and if efficacy is established it would be most appropriate to administer at early disease stages, before dementia becomes established.	Thank you for your comment. NICE can only appraise technologies that have a marketing authorisation. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Alzheimer's Research UK	There are currently no technologies available that delay or prevent the progression of Alzheimer's disease. Biogen have filed for FDA approval of aducanumab, therefore this could be the first in class disease modifier. 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 patient population that is currently underserved.	Thank you for your comment. Comment noted. No action required.
	RICE	Should the FDA approve Aducanumab in November then there will be pressure for it also to be approved in Europe and, if it is so approved, then it will become an important topic for NICE to consider	Thank you for your comment. Comment noted. No action required.
Wording	Biogen	The draft remit is not aligned with the population(s) in the draft scope table. Biogen would like to rephrase the draft remit to read "To appraise the clinical and cost effectiveness of aducanumab for treating mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD."	Thank you for your comments. The remit has been updated based on feedback from scoping workshop.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	"Behavioural and neuropsychiatric" symptoms captures the non-cognitive problems more fully than just "behavioural", since not all non-cognitive symptoms manifest as changes in behaviour	Thank you for your comment. Comment noted. No action required.
	Alzheimer's Research UK	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	RICE	Yes although a lot may depend on the exact wording of any licensed approval	Thank you for your comment. No action required.
Timing Issues	Biogen	There is a high unmet need for a disease modifying therapy (DMT) that treats the underlying cause of AD. Aducanumab has the potential to be the first treatment to target the underlying amyloid beta pathology of AD (subject to regulatory approval). A timely decision following market authorisation and licensing of aducanumab will ensure that appropriate patients should not face any unnecessary delays.	Thank you for your comment. Comment noted. No action required.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	Very urgent, as the first potential disease modifying drug this could have very high impact, but should only be considered if marketing authorisation is given.	Thank you for your comment. Comment noted. No action required.
	Alzheimer's Research UK	Aducanumab has filed with FDA for regulatory approval, with a decision anticipated by March 2021. Alzheimer's disease is a leading cause of death in England, and therefore any technology which can slow or delay disease progression should be considered for cost-effectiveness as a matter of urgency	Thank you for your comment. Comment noted. No action required.
	RICE	This will depend on the approval process in the US and in Europe but it could become urgent and therefore the scoping workshop is very appropriate	Thank you for your comment. Comment noted. No action required.
	Biogen	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	Eisai	No comments	No action required.
	British Association for Psychopharmacology	I am presuming that the comparison will be aducanumab + standard care v standard care, rather than aducanumab v standard care. The comparison between aducanumab v standard care does not seem of relevance, because non-one would not give standard care and because for mild cognitive impairment standard care is really around education, support and lifestyle advice, no drugs are licensed for the condition.	Thank you for your comment. Comment noted. Scope updated to reflect intervention in the PICO table as 'Aducanumab plus best supportive care.'
	Alzheimer's Research UK	No comments	No action required.
	RICE	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Biogen	**The background information states that "The recorded number of people diagnosed with dementia in England was 471,000 in February 2020.3 Therefore, the number of people diagnosed with AD could be up to 329,700."** **Comment/response:** Whilst this estimate is aligned with the diagnosis rates for AD by PHE, these data do not include patients with MCI due to AD. According to the AGE UK report on "Dementia and cognitive decline", the prevalence of MCI in general is estimated at between 5% and 20% in the older	Thank you for your comment – the background section has been revised.

Section	Consultee/ Commentator	Comments [sic]	Action
		population (above 65 yrs. old), which equates to between 0.5 million and 2 million people in the UK [1]. Furthermore, the overall numbers of dementia cases in the draft scope are lower than those reported by the Alzheimer's Society, which estimated that in 2019, there were 748,000 people with dementia in England. Of those, an estimated 107,100 people had mild AD. By 2040, both numbers are projected to rise to 1,352,400 people suffering from dementia (81% increase), and 166,700 people suffering from mild AD (56% increase) [2, 3]. Moreover, as acknowledged by NICE, it is estimated that about 200,000 people in England are undiagnosed with dementia [4]. The number of patients with AD estimated by both PHE and Alzheimer's Society include patients with moderate and severe AD. These patients are not within the scope of this technology appraisal. Whilst there are a large number of patients, it is important for NICE to understand that not all of the estimated cases of MCI due to AD and mild AD are expected to be treated with aducanumab. In addition to presenting to the healthcare system for a diagnosis of AD, a positive test for amyloid beta is required to be a candidate for treatment. **The background information states "Current management involves the treatment of cognitive, non-cognitive and behavioural symptoms. NICE guidance (TA217 and NG97) recommends acetylcholinesterase (AChE) inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease and memantine as an option for managing severe Alzheimer's disease or for people with moderate**	Thank you for your comment – the background section has been revised.

		Alzheimer's disease who are intolerant or have a contraindication to AChE inhibitors." **Comment/response:** Please consider the following points to ensure that provided background information presents an accurate overview of the AD pharmacological treatment landscape: • The recommended treatments in the NICE guidance do not treat the disease itself but, rather, provide patients with AD with short-term, symptomatic relief. As such, they are not DMTs, and are more accurately described as symptomatic therapies or as best supportive care (BSC), as they do not alter the course of the disease • Over the course of the disease, as the treatment effect of each therapy is no longer durable, patients need to be switched to alternative therapies in order to maintain amelioration of symptoms • Aducanumab has the potential to be the first DMT (subject to regulatory approval) developed to alter the clinical course of AD. By slowing disease progression, aducanumab reduces the cognitive and functional decline in AD patients • This is achieved through the unique mechanism of action of aducanumab (high affinity binding to aggregated amyloid beta), which has shown to promote clearance of neuropathological amyloid beta plaques • Thus aducanumab exerts early effects that interrupt the initiation of the pathophysiological processes that lead to irreversible neurodegeneration • Whereas current symptomatic therapies manage symptoms in the mild to severe AD stages, aducanumab has the potential to	

Section	Consultee/ Commentator	Comments [sic]	Action
		be the first therapy indicated for MCI due to AD and mild AD (subject to regulatory approval) • Further, in clinical trials of aducanumab, patients received aducanumab plus BSC, which included use of symptomatic treatments **Comment/response:** **The background information states that "Non-pharmacological treatment includes (…), day centres, respite care and care homes."** Please consider the following points to ensure that provided background information presents an accurate overview of the AD non-pharmacological treatment landscape: • The draft label population for aducanumab includes patients with MCI due to AD and mild AD • Non-pharmacological treatments such as day centres, respite care and care homes should not be considered, as they predominatnly apply to patients who have progressed to more severe AD stages, and are not the target population for aducanumab	Thank you for your comments. According to attendees at the scoping workshop, some patients with MCI or mild dementia due to Alzheimer's disease may receive non-pharmacological care. No changes made.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Alzheimer's Research UK	No comments	No action required.
	RICE	I think that the figure for MCI in the over 65s should be 5-20% (as per the Alzheimer's Society website). The prevalence rates are very much affected by the source of the population being assessed and in the general population as opposed to, for example, memory clinic populations, the prevalence reported is lower. I was not able to access the reference that you quoted for this, to see where they obtained their 10-20% figure from.	Thank you for your comments. The prevalence of MCI has been updated in the draft scope.
The technology/ intervention	Biogen	Please consider the following points to ensure the description of the technology is accurate: • Aducanumab is a human monoclonal antibody against amyloid beta • Aducanumab will have the brand name of "ADUHELM" • Aducanumab will be delivered every 4 weeks via intravenous infusion	Thank you for your comments. The technology description has been updated to reflect it is a 'monoclonal' antibody.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	No comments	No action required.
	Alzheimer's Research UK	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	RICE	Yes	Thank you for your comment. Comment noted. No action required.
Population	Biogen	Aducanumab is anticipated to be recommended for people with MCI due to AD or mild AD with confirmed amyloid beta pathology	Thank you for your comments. The scope population has been updated based on feedback from the scoping workshop.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	Because there are established treatments for Alzheimer's disease but not MCI there may be a case for considering these groups separately for some analyses. On the other hand, the expert field agrees that MCI due to AD and early AD are on a continuum, and the point at when the threshold for dementia is reached is sometimes hard to define.	Thank you for your comments. The scope population has been updated based on feedback from the scoping workshop.
	Alzheimer's Research UK	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 comments. The scope population has been updated based on feedback from the scoping workshop.

Section	Consultee/ Commentator	Comments [sic]	Action
	RICE	The real issue will be identifying people with MCI due to Alzheimer's disease and who probably, by definition, will need evidence of potential amyloid accumulation in the brain	Thank you for your comments. The scope population has been updated based on feedback from the scoping workshop.
Comparators	Biogen	The draft scope states the following comparators: "Established clinical management without aducanumab including but not limited to: • acetylcholinesterase (AChE) inhibitors ○ donepezil, galantamine and rivastigmine • memantine • non-pharmacological management" **Comment/response:** Please consider the following points to ensure that the most accurate comparators are used in the evaluation: • Biogen requests that "BSC" or "SoC", rather than specific interventions should be used as a comparator • Aducanumab is not envisaged to replace symptomatic or non-pharmacological treatments. Aducanumab-treated patients should continue to receive symptomatic and non-pharmacological management as required, as per the pivotal clinical trials	Thank you for your comments. The comparators in the scope have been updated based on feedback from the scoping workshop.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Non-pharmacological management should also be removed from the comparator list as outlined in the Questions for consultation section • Additionally, Biogen requests that memantine be removed from the list of symptomatic treatments. As per Background information and NICE guideline NG97 Section 1.5.2 (published in June 2018), memantine monotherapy is recommended as an option for managing moderate AD patients intolerant to AChE inhibitors or severe AD patients [5] • Biogen would also like to emphasise that given the innovative mechanism of action and the treatment objectives of aducanumab, AChE inhibitors cannot be considered as appropriate comparators for aducanumab • This is supported by the EMA label for AChE inhibitors which specify their role in the alleviation of symptoms rather than the treatment of disease. The EU label states that these treatments are indicated for the “symptomatic treatment of AD” or the “treatment of dementia of the AD type”, while the clinical pharmacology section of the label states that they cannot be considered to have any effect on the underlying dementia process or disease progression [6-11] • Aducanumab has the potential to be the first therapy indicated for MCI due to AD and mild AD dementia (subject to regulatory approval). It aims to tackle the disease before dementia symptoms take hold or are in the early stages. Therefore, aducanumab has a small overlapping target population with AChE inhibitors with regards to the treatment of mild AD dementia but has no overlap with memantine	

Section	Consultee/ Commentator	Comments [sic]	Action
	Eisai	Aducanumab would be the first disease modifying treatment for patients with early Alzheimer's' disease. The treatments currently listed in the draft scope, including acetylcholinesterase inhibitors (AChEIs) manage symptoms only and are therefore not alternative disease modifying treatments. Please also see response to questions for consultation.	Thank you for your comments. The comparators in the scope have been updated based on feedback from the scoping workshop.
	British Association for Psychopharmacology	Please see comment above. Because much of standard care is supportive, and this is the first putative disease modifier (as opposed to helping symptoms), one would not withdraw this supportive care if aducanumab was available, so it is not really a comparator. Cognitive Stimulation therapy is widely used and NICE recommended but missing from the list of standard care.	Thank you for your comments. The comparators in the scope have been updated based on feedback from the scoping workshop.
	Alzheimer's Research UK	The current comparators are recommended for people diagnosed with mild Alzheimer's (NICE 2018) but there are no established clinical guidelines in the UK regarding use of AChE inhibitors or memantine for the mild cognitive impairment population for people with MCI due to Alzheimer's disease.	Thank you for your comments. The comparators in the scope have been updated based on feedback from the scoping workshop.
	RICE	Souvenaid, the medical food from Nutricia has been studied with some positive results in the MCI group and this probably should at least be considered	Thank you for your comments. The comparators in the scope have been updated based on

Section	Consultee/ Commentator	Comments [sic]	Action
			feedback from the scoping workshop.
Outcomes	Biogen	Biogen requests that the following outcomes are to be added: • Cognitive & functional impairment (CDR-SB) • Disease progression biomarkers • Functional impairment • Health-related quality of life (HRQoL) of the patient and the carer, including Activities of Daily Living (ADL) These outcomes are important in demonstrating the clinical effect of aducanumab in patients with AD. Additionally, Biogen would like to emphasise that as the potential first DMT in the AD treatment landscape, aducanumab could be the only treatment that can significantly change the course of the disease by preserving baseline functioning and preventing or slowing down the cognitive and behavioural decline often experienced by AD patients.	Thank you for your comments. The scope outcomes have been updated based on feedback from the scoping workshop. Please note that the list of outcomes in the draft scope is non-exhaustive.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	Yes	Thank you for your comments. No action required.
	Alzheimer's Research UK	This scope should take into account the impact of Alzheimer's on carers health related quality of life as an outcome. In previous NICE assessments of symptomatic treatments for Alzheimer's NICE included carer quality of life. We know the majority of dementia costs per year are due to informal care at £11.6bn, a significant proportion of this will	Thank you for your comments. The scope outcomes have been updated based on

Section	Consultee/ Commentator	Comments [sic]	Action
		include carers of people living with Alzheimer's. As well as having a major impact on daily living activities we also know informal carers are at significant risk of depression and anxiety. Given the impact that Alzheimer's disease has beyond the person with the disease, and especially on carers, we believe carer health related quality of life should be considered in a future appraisal to accurately assess the full value of this treatment.	feedback from the scoping workshop. Please note that the list of outcomes in the draft scope is non-exhaustive.
	RICE	A delay in the progression to dementia due to AD would be another outcome to consider	Thank you for your comments. The scope outcomes have been updated based on feedback from the scoping workshop. Please note that the list of outcomes in the draft scope is non-exhaustive.
Economic analysis	Biogen	Economic analysis states: "Costs will be considered from an NHS and Personal Social Services perspective." **Comment/response:** The economic burden of AD is much broader than the impact on healthcare and social care systems. A report from the London School of Economics, "Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019–2040," estimates that the total costs of dementia care in England in 2019 were £29.5 billion, of which 14% is attributable to healthcare, 46% is attributable to social	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 the Guide to the methods of

Section	Consultee/ Commentator	Comments [sic]	Action
		care, and 40% is attributable to unpaid care. This highlights an inherent gap in care, in which an effective medical therapy is missing, and the financial burden of AD falls on the social care and informal care of AD, rather than the medical treatment and prevention of AD [3]. Furthermore, aducanumab has the potential to be the first DMT for AD. Currently used value assessment frameworks are sub-optimal in demonstrating the full benefits of new DMTs, which span beyond the scope of healthcare systems, and are unlikely to be captured within the clinical trial setup. For example, AD is a continuum, and as the severity of AD increases, patients need increasing levels of support. Any delay or halt in disease progression resulting from novel DMT can lessen patients' care needs and the costs associated with the care received, as well as decrease the burden on the caregivers. DMTs can therefore relieve the economic burden posed to caregivers and social care systems by instigating a shift from indirect and social care costs toward direct medical costs. Additionally, there are several macroeconomic consequences of AD, such as productivity losses and reduction in output from employees taking time off to cope with the impact of AD, reduced wages that lead to reduced market consumption, lower saving rates, lower rates of return on capital, and lower levels of domestic and foreign investments, all of which hamper the economic growth of societies [12].	technology appraisal. No action required.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	Agree the time horizon needs to be long (many years) but it will be a challenge to determine exactly how long as it depends on a) how long the treatment is given for and b) if and how long the effects last once treatment has stopped	Thank you for your comment. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Alzheimer's Research UK	No comments	No action required.
	RICE	The costs of MCI are relatively low compared with the costs of dementia and so a long enough time frame needs to be considered to pick up potential benefit of reduced cognitive deterioration and delayed diagnosis of dementia	Thank you for your comment. Comment noted. No action required.
Equality and Diversity	Biogen	No equality issues have been identified. However, Biogen would like to emphasise that differences in adoption of service (e.g. related to differential geographic coverage of imaging facilities, differences in access to specialist care) may lead to a "postcode lottery" effect and result in inconsistent access to diagnosis and treatment among patients across England. Further, given that AD mainly affects people over the age of 65, patients have less opportunity to benefit from QALY gains from treatment than in many other disease areas [13]. Additionally, AD disproportionally affects women over men, and most family carers of people with dementia are women [14, 15]. Please refer to the *Questions for consultation* section	Thank you for your comment. Comment noted. No action required.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	No comments	No action required.
	Alzheimer's Research UK	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	RICE	No comments	No action required.
Other considerations	Biogen	No further comments	No action required.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	No comments	No action required.
	Alzheimer's Research UK	No comments	No action required.
	RICE	A major issue will be identifying people with MCI due to AD as mentioned above. It would be expected that only people with evidence supportive of amyloid accumulation in the brain could benefit from the treatment. This would currently need to be confirmed either after CSF analysis for amyloid, tau and phosphotau or by amyloid PET examination. Neither of these approaches are currently widely available. The potential arrival in the future of blood-based biomarkers would potentially make this simpler.	Thank you for your comments. Comments noted. The scope population has been updated based on feedback from the scoping workshop.
Innovation	Biogen	Yes, aducanumab (ADUHELM®) is considered a step change therapy. There has been a long-standing unmet need for a DMT for patients with AD. Aducanumab has the potential to be a first-in-class molecule that is clearly distinguished from symptomatic therapies in both its design and mechanism of action. The symptomatic therapies are all small-molecule compounds that aim to temporarily alleviate the dementia symptoms associated with AD through stimulating neuronal receptor functions. Unlike symptomatic therapies, aducanumab is a human monoclonal antibody, and has the potential to be the first DMT that can produce a	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		significant change in the clinical progression of AD by interrupting the underlying pathophysiological mechanisms that lead to neurodegeneration. On account of its strong and selective binding affinity for aggregated amyloid beta, aducanumab promotes clearance of amyloid beta plaques and slows progression of downstream pathological processes, such as accumulation of tau levels, therefore preserving baseline abilities of AD patients. Please refer to the *Comparators* section. Biogen would like to emphasise that, as outlined in the *Economic analysis section*, aducanumab is predicted to bring significant added value to AD treatment landscape, which is unlikely to be captured by current QALY calculation framework. For example, it is increasingly recognised that currently measured societal costs represent only a proportion of the total burden of dementia and AD, or the so-called “tip of the iceberg”. Most studies assessing the costs of dementia and AD focus on patients with a dementia diagnosis and generally demonstrate that costs increase with disease severity. However, these studies do not fully capture the total impact of AD. Firstly, the magnitude of indirect costs (e.g., lost productivity, informal caregiving) can vary widely depending on the methodologies and assumptions used. Second, cost of illness studies may not be measuring the full spectrum of AD costs; for example, financial impacts on households (e.g., reduced savings, financial exploitation, out-of-pocket costs, unemployment) may have substantial and intergenerational effects on the economy. Finally, some studies suggest that costs begin to accrue years before a dementia diagnosis, albeit at a comparatively lower rate than those in advanced disease stages. However, given the long preclinical stage (~10–20 years before the onset of symptoms), it is possible that these ‘hidden costs’ represent a substantial fraction of cumulative AD costs [16].	

Section	Consultee/ Commentator	Comments [sic]	Action
	Eisai	If approved, aducanumab would be the first disease modifying treatment for patients with early Alzheimer's' disease. This would represent a step change in that it would be the first treatment to target the underlying disease pathology rather than symptom relief of the more advanced disease state associated with existing treatments. It is important to consider the burden that Alzheimer's disease places, not just on the patient, but also family members or those close to the patient who often take on the caregiver role. The QALY represents quality of life on a patient level and captures improvements in health outcomes and associated direct medical costs on an individual level but does not account for any health-related benefits experienced by caregivers. We believe that, considering the immense toll Alzheimer's' disease places on caregivers and family members, any health related and economic benefits associated with individuals in these roles should be explored and considered as part of the appraisal process.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No change to scope.
	British Association for Psychopharmacology	This is a highly innovative treatment with potential to make a step change in terms of being the first disease modifying treatment for dementia. Calculation of QALYs for people with dementia is known to be highly challenging.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No change to scope.
	Alzheimer's Research UK	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*	Thank you for your comment. The extent to which the technology may be innovative will be considered in any

Section	Consultee/ Commentator	Comments [sic]	Action
		By 2025, there will be over 1 million people living with dementia in the UK. Currently, there are no treatments that can delay the onset or slow the progression of the diseases that cause dementia. This treatment is an anti-amyloid therapy, so innovative in nature, first in it's class with no direct comparator. If it is proven to be clinically and cost effective, aducanumab would be a step-change in the management of the Alzheimer's in the early stages of the disease. *Do you consider that the use of the technology can result in any potential significant and 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.	appraisal of the technology. No change to scope.
	RICE	There has been some doubt about the efficacy of aducanumab and initially trials with the compound were halted because of this. Regulatory reviews will be assessing the latest analysis of this data and if the results are thought to convincingly demonstrate efficacy then it will be considered as a stepchange as the first antiamyloid therapy to achieve such efficacy.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		There may be difficulties in QALY calculations since the cost implications of MCI are relatively low and the benefit is in a long-term reduction in cognitive decline and the onset of dementia	
Questions for consultation	Biogen	**Have all relevant comparators for aducanumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment caused by Alzheimer's disease?** **Comment/response:** Biogen wish to highlight that currently NICE do not define a treatment pathway for patients with MCI due to AD and as of today, no pharmacological treatments are available to treat MCI due to AD. Additionally, many patients with MCI due to AD do not receive the diagnosis. Therefore it is impossible to outline "established clinical practice in the NHS" for MCI due to AD. Some non-pharmacological treatments including diet, exercise, cognitive training, could be considered, though it is difficult to estimate to what extent they are used in clinical practice. Additionally, there is a lack of double-blinded, randomised studies that compare drug treatment with non-pharmacologic treatments Biogen requests that "best supportive care" or "standard of care", rather than specific interventions should be used as a comparator. Symptomatic and non-pharmacological management should be considered add-ons to aducanumab, as per clinical trials of aducanumab. **How should non-pharmacological management be defined?** **Comment/response:**	Thank you for your comments. Comments noted. The scope comparators have been updated based on feedback from the scoping workshop. Thank you for your comments. Comments

Section	Consultee/ Commentator	Comments [sic]	Action
		Non-pharmacological management stems from a variety of disciplines, each attempting to positively influence cognition, mood, and other behavioural and psychological symptoms of dementia. These methods include techniques such as reality orientation (activities to orient individuals to time and place), reminiscence therapy (eliciting recall of past events), validation therapy (focused on alleviating stress, promoting contentment, and decreasing behavioural disturbances), and cognitive stimulation (using tasks and activities, including word games and puzzles) [17], and may also include other aspects such as diet and exercise. As MCI is excluded from the scope of the NICE guideline NG97 (published in June 2018), guidance on non-pharmacological management for MCI due to AD is not specifically provided. In general, it is assumed that these patients will be followed up through a “watch and wait” approach and given lifestyle advice. For AD, non-pharmacological management may also include personal care. Biogen considers care as a resource for disease management, rather than as a comparator. As discussed above, day centres, respite care and care homes are more relevant to the moderate/severe AD health states in an economic model.	noted. The scope comparators have been updated based on feedback from the scoping workshop.
		Are there any subgroups of people in whom aducanumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? **Comment/response:** The primary and secondary efficacy endpoints for the EMERGE study were analysed by subgroups, as per the statistical analysis plan and were also assessed by post-hoc analyses. Taken together, the	Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		subgroup results for the aducanumab high-dose treatment group are consistent across demographics and baseline characteristics (that is, both in patients with MCI due to AD and mild AD) with the primary analyses of EMERGE study and support a positive treatment effect of aducanumab in the entire assessed population. **Where do you consider aducanumab will fit into the existing NICE pathway?** **Comment/response:** Biogen wish to highlight that currently NICE do not define a treatment pathway for patients with MCI due to AD and therefore it is not possible to place aducanumab within an existing UK treatment pathway for AD. The existing NICE guideline NG97 (published in June 2018) focuses on pharmacological treatment for mild, moderate and severe AD. Following a positive reimbursement decision, a new category for pharmacological treatment of MCI due to AD will need to be created. Initiation of aducanumab soon after diagnosis of MCI due to AD would therefore be considered a step change therapy. Further, once approved aducanumab has the potential to improve the quality of life for those with dementia. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** **Comment/response:**	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Aducanumab is a monoclonal antibody to be delivered every 4 weeks via intravenous infusion and is intended to be given to patients with a positive diagnosis of AD. Biogen is aware of the limited diagnostic and infusion capacity in England. Given the potential size of the eligible patient population, Biogen is concerned that variations in service provisions will mean that patients eligible for treatment with aducanumab will be unable to access treatment due to limited CSF testing and/or PET scans for the diagnosis of AD, and due to subsequent limitations in infusion facilities. There is considerable variation in both testing facilities and infusion capacity across England. As indicated by independent reports by Mattke et al. and Hlavka et al., as well as the 2019 national memory service audit, several aspects of the UK healthcare system landscape raise concerns [18-20]: • Limited density of general practitioners (GPs) compared to EU5 countries – in 2016, UK had 0.76 GPs per 1,000 population • The UK has comparatively low number of dementia specialists – estimated 8.0 specialists (neurologists, geriatricians, geriatric psychiatrists) per 100,000 population • Geographic coverage with cyclotron facilities to produce the ligand for PET scans is sufficient with gaps in South-Western England, but PET capacity is quite limited – 0.5 PET scanners per 1M population • Potential geographical obstacles to access in areas like Western England • PET scanners are largely reserved for oncologic cases, whereas use in Alzheimer's patients is exceedingly uncommon outside of clinical trials	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Despite being included a recommendation within the NICE guideline for dementia (NG97), lumbar punctures for CSF testing are also uncommon in routine care • Supportive guidance from NICE and allocation of funding would be a precondition to increase testing capacity. Given the high investment and unit cost of PET scans, the expansion of biomarker testing capacity is likely to rely on CSF testing • The relatively low density of MRI scanners combined with a high utilization rate in the UK suggests that MRI capacity might constitute a bottleneck – 9.46 MRI scanners per 1M population and 7,973 annual MRI scans per device (second highest utilization rate in EU5) • The average wait times for a dementia specialist visit and infusion treatment in the UK are currently ~13 and ~14 months respectively. Due to limited capacity for specialist visits and infusions, the backlog of patients awaiting diagnosis and infusion treatment is predicted to clear as late as 2042 In the current coronavirus (COVID-19) pandemic there is a general increase in demand for healthcare services, which places potential system constraints on the ability to manage patients with AD. There are also constraints on the social care system to manage patients with dementia as a result of the pandemic. Since the lockdown on 23 March, the Alzheimer's Society has reported that family and friends have as a result spent an extra 92 million hours caring for loved ones with dementia (as of September 2020) [21]. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.	

Section	Consultee/ Commentator	Comments [sic]	Action
		(Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). **Comment/response:** This is appropriate	
	Eisai	Have all relevant comparators for aducanumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for mild cognitive impairment caused by Alzheimer's disease? In the UK, patients with mild cognitive impairment with an underlying Alzheimer's' disease pathology typically would not undergo active treatment, as there are currently no licensed treatments for this stage in the disease. The majority of patients with MCI due to AD are expected to be undiagnosed. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. As mentioned above, it is expected that currently the majority of patients with mild cognitive impairment with an underlying Alzheimer's' disease pathology are undiagnosed. Clinical diagnosis most frequently occurs when patients progress to mild Alzheimer's' disease or more severe disease stages. Many patients with a diagnosis of Alzheimer's disease based on clinical scales currently do not have their diagnosis confirmed as positive amyloid pathology. This is due to the complexities associated with obtaining a clinical confirmation of amyloid pathology, which requires a PET scan or cerebral spinal fluid testing. This is most	Thank you for your comments. Comments noted. The scope comparators have been updated based on feedback from the scoping workshop. Thank you for your comments. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		likely due to a combination of resource constraints as well as the current lack of clinical value an amyloid positive diagnosis provides. These factors are likely to pose significant barriers to the adoption of a new disease modifying treatment for Alzheimer's disease, since patients must be diagnosed in the early disease stages and have their diagnosis confirmed as amyloid positive prior to initiation of any treatment.	
	British Association for Psychopharmacology	Aducanumab would not be considered as an alternative to cholinesterase inhibitors as a) it may be given early, at a disease stage where current anti-dementia drugs are not licensed and b) it has a quite different mechanism of action, and anti-amyloid therapy aimed at modifying the underlying disease process, as opposed to the current generation of symptomatic transmitter replacement drugs. If approved Aducanumab would likely be given early and first, with symptomatic treatments reserved for when the stage of mild-moderate dementia reach is reached.	Thank you for your comments. Comments noted.
	Alzheimer's Research UK	*Where do you consider aducanumab will fit into the existing NICE pathway, Dementia?* • It is likely that if aducanumab is made clinically available in England a new clinical pathway would need to be developed. • 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. Biomarkers currently available include PET amyloid scanning and CSF sample via lumbar puncture. These are not currently commissioned as routine diagnostics across services	Thank you for your comments. Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		in England. Access to these diagnostics is particularly difficult for Memory Assessment Services, which are predominantly led by Psychiatrists in Mental Health Trusts. • 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. • Aducanumab would also significantly alter the treatment component of the pathway in terms of drug delivery and ongoing monitoring of patients. *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* • There will be significant service delivery impacts for the diagnostics and treatment components of the pathway which could be barriers to adoption. Support to increase 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.	Thank you for your comments. Comments noted.
	RICE	In addition to the potential need for more sophisticated (and costly) diagnostic tools to confirm MCI due to AD, the treatment is given intravenously, which will be a new innovation in this area. Neither CSF sampling nor iv therapy are realistic for the majority of memory clinics based in old-age psychiatry settings so this may also require novel approaches (recognised area treatment centres for example).	Thank you for your comments. Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Biogen	No additional comments	No action required.
	Eisai	No comments	No action required.
	British Association for Psychopharmacology	No	No action required.
	Alzheimer's Research UK	No comments	No action required.
	RICE	No comments	No action required.

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

NHSE & I